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Structural studies on sulfonylbicyclo[*n*.2.0]alkan-1-ols

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ABSTRACT: The structures of a series of sulfonylbicyclo[*n*.2.0]alkan-1-ols (*n* = 3–6) **1**–**6** were determined by single-crystal x-ray diffraction. A survey of the Cambridge Structural Database and Monte Carlo conformational searches using MacroModel were performed. Compounds **1**, **3** and **4** show intramolecular hydrogen bonding. Compound **2** is stabilized by three-centered 'bifurcated' intra- and intermolecular hydrogen bonds between the hydroxyl proton and the sulfone oxygens. Compounds **5** and **6** are stabilized by intermolecular hydrogen bonds formed between the *trans* 1-hydroxy and sulfonyl moieties. In compounds **1**–**6**, the degree of cyclotorsion of the four- five-, six-, seven- and eight-membered rings adjacent to the bond between the bridgehead atoms C1 and C4 is reflected in the magnitude about the exterior angles about C1 (C2—C1—C*x*) and C4 (C3—C4—C5). The six-membered ring systems of **2**, **5** and **6** showed noteworthy increases in the C5—C4—C1—C*x* and C3—C4—C1—C2 torsion angles, and this was attributed to the conformational constraints of the pseudo-chair conformation of the six-membered ring. Similar conformational structure effects were observed in the modeled structures **1a**–**6a** to those observed for the x-ray structures **1**–**6**. Copyright © 2002 John Wiley & Sons, Ltd.
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KEYWORDS: bicyclo[*n*.2.0]alkan-1-ol; β-hydroxy sulfone; cyclobutanol; hydrogen bonding; x-ray crystallography; Cambridge Structural Database analysis; Monte Carlo conformational search

INTRODUCTION

Cyclobutanols present in polyfunctional ring systems are versatile intermediates in organic synthesis,[1] the synthesis of natural products[2] and bioactive compounds[3] and have been the subject of a number of mechanistic and structural studies.[4,5] During the course of our investigations on the synthesis of fused-ring natural products, we accessed a range of simple bicyclo[*n*.2.0]alkanols. First, from the convergent and expedient reaction between the lithium enolate of cyclohexanone and (±)-phenyl vinyl sulfoxide under controlled conditions, we obtained 8-phenylsulfinyl bicyclo[4.2.0]octan-1-ol as a mixture of diastereomers, in conjunction with small amounts of the expected monoalkylated product. Subsequently, we extended the scope of this study to include the lithium enolates of cyclopentanone, cycloheptanone and cyclooctanone and the reaction of *p*-tolyl vinyl sulfoxide with the lithium enolate of cyclohexanone. Thus the constraints for simple bicyclo[*n*.2.0]alkanols formed from readily available ketones were explored. The results of these synthetic studies are reported elsewhere.[6] In the course of this work, we oxidized a number of these sulfoxides to the corresponding sulfone derivatives with *m*-chloroperbenzoic acid (*m*-CPBA) or Oxone to yield crystalline products which were characterized by single-crystal x-ray crystallography. A survey of the Cambridge Structural Database (CSD) showed that only limited structural data were available for bicyclo[*n*.2.0]alkan-1-ols (*n* = 3–6) and that these structures were present only in polycyclic systems derived from natural products[7] or synthetic studies[8] and conformationally constrained polycyclic systems.[9] The current work, the results of which we report here, thus represents a study of the structural constraints in simple bicyclo[*n*.2.0]alkanols (where *n* = 3–6).

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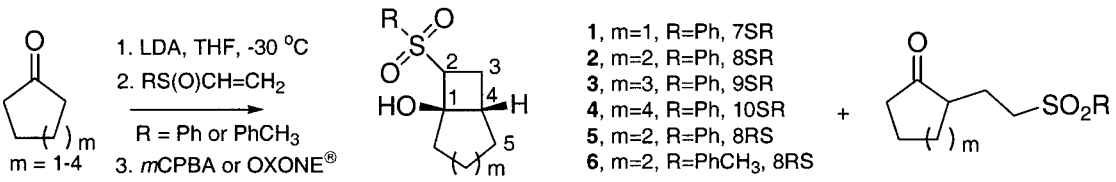
EXPERIMENTAL

Sample preparation

Bicyclo[*n*.2.0]alkanols (*n* = 3–6) as sulfoxide derivatives were obtained, as described elsewhere,[6] by the reaction of the lithium enolate of cyclopentanone, cyclohexanone, cycloheptanone or cyclooctanone in THF under nitrogen at −30 °C with phenyl vinyl sulfoxide followed by warming at 0 °C for 45 min and by the reaction of the lithium enolate of cyclohexanone in THF under nitrogen



Scheme 1

at −30 °C with (*R*)-(+)-*p*-tolyl vinyl sulfoxide for 5 min. The crude sulfoxide mixtures for cyclopentanone, cycloheptanone or cyclooctanone were oxidized to the corresponding sulfones with *m*-CPBA. (1*RS*,5*SR*,7*SR*)-7-(Phenylsulfonyl)bicyclo[3.2.0]heptan-1-ol (**1**) and (1*RS*,7*SR*,9*SR*)-9-(phenylsulfony)bicyclo[5.2.0]nonan-1-ol (**3**) were isolated by column chromatography (40:60 ethyl acetate–hexane) followed by HPLC [25:75 ethyl acetate–hexane (**1**) or 40:60 ethyl acetate–hexane (**3**)]. (1*RS*,8*SR*,10*SR*)-10-(Phenylsulfonyl)bicyclo[6.2.0]decan-1-ol (**4**) was isolated by column chromatography (30:70 ethyl acetate–hexane) followed by HPLC (30:70 ethyl acetate–hexane). Slow diffusion of diethyl ether into a solution of compound **1**, **3** or **4** in dichloromethane gave well formed crystals suitable for x-ray diffraction of **1** (m.p. 362.1–365.6 K), **3** (m.p. 372.3–374.1 K) and **4** (m.p. 371.1–373.2 K).

For the reaction of cyclohexanone with phenyl or *p*-tolyl vinyl sulfoxide, the crude sulfoxide bicyclooctanol was isolated by column chromatography (4% propan-2-ol in dichloromethane), recrystallized from diethyl ether and oxidized with *m*-CPBA (**2**, **6**) or Oxone (**5**). Recrystallization of (1*RS*,6*SR*,8*SR*)-8-(phenylsulfonyl)-bicyclo[4.2.0]octan-1-ol (**2**), (1*SR*,6*SR*,8*RS*)-8-(phenylsulfonyl)bicyclo[4.2.0]octan-1-ol (**5**) and (1*RS*,6*SR*,8*RS*)-8-[(4′-methylphenyl)sulfonyl]bicyclo[4.2.0]octan-1-ol (**6**) from diethyl ether gave well formed crystals suitable for x-ray diffraction of **2** (m.p. 363–365 K), **5** (m.p. 405–407 K) and **6** (m.p. 412–414 K).

Compound physical data

The physical data for **2** and **5** and general instrumentation have been reported elsewhere.[6]

(1RS,5SR,7SR)-7-(Phenylsulfonyl)bicyclo[3.2.0]heptan-1-ol (1). Anal. Calcd for $C_{13}H_{16}SO_3$: C, 61.87; H, 6.39. Found: C, 61.82; H, 6.34%. IR, ν_{max} (KBr) (cm^{-1}): 3536 (OH), 1291 (SO_2), 1144 (SO_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92–7.99, m, 2H, *o*-C_6H_5; 7.60–7.68, m, 1H, *p*-C_6H_5; 7.51–7.60, m, 2H, *m*-C_6H_5; 3.62, ddd, 1H, $J_{7,6}$ 9.5, $J_{7,6}$ 5.5, $J_{7,5}$ <1, H7; 3.40, br s, 1H, $W_{h/2}$ 136, OH; 2.62–2.72, m, 2H, H5, H6; 1.74–1.89, m, 2H, H3, H4; 1.60–1.84, m, 3H, H3, 2 × H2; 1.46–1.60, m, 2H, H4, H6. ^{13}C NMR (50 MHz, $CDCl_3$): δ 139.5 *i*-C_6H_5; 133.6 *p*-C_6H_5; 129.2 *m*-C_6H_5; 127.9 *o*-C_6H_5; 83.6 C1; 64.2 C7; 46.3 C5; 40.1 C2; 31.4 C4; 24.2 C3; 20.1 C6. $ESMS^+$: *m/z* 259 (MLi^+, 100), 275 (MNa^+, 30).

(1RS,7SR,9SR)-9-(Phenylsulfonyl)bicyclo[5.2.0]nonan-1-ol (3). Anal. Calcd for $C_{15}H_{20}SO_3$: C, 64.25; H, 7.19; S, 11.43. Found C, 64.34; H, 7.26; S, 11.21%. IR ν_{max} (KBr) (cm^{-1}): 3505, (OH), 1307, (SO_2). 1148, (SO_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84–7.98, m, 2H, *o*-C_6H_5; 7.57–7.67, m, 1H, *p*-C_6H_5; 7.48–7.57, m, 2H, *m*-C_6H_5; 3.72, br s, 1H, $W_{h/2}$ 36, OH; 3.53, ddd, 1 H, $J_{9,8}$ = 9.5, $J_{9,8}$ 5.5, $J_{9,7}$ 1, H9; 2.48–2.66, m, 2H, H7, H8; 1.80–1.92, 1H, H6; 1.54–1.80, m, 6H, 2 × H2, H3, H4, H5, H8; 1.42–1.54, m, 1H, H3 or H4; 1.10–1.34, m, 3H, H3 or H4, H5, H6. ^{13}C NMR (50 MHz, $CDCl_3$): δ 139.6 *i*-C_6H_5; 133.4 *p*-C_6H_5; 129.0 *m*-C_6H_5; 127.9 *o*-C_6H_5; 78.9 C1; 64.1 C9; 48.7 C7; 38.8 C2; 33.6 C6; 31.8 C3 or C4; 27.6 C5; 23.5 C3 or C4; 21.7 C8. $ESMS^+$: *m/z* 287 (MLi^+, 100), 303 (MNa^+, 100).

(1RS,8SR,10SR)-10-(Phenylsulfonyl)bicyclo[6.2.0]decan-1-ol (4). Anal. Calcd for $C_{16}H_{22}SO_3$: C, 65.26; H, 7.53; S, 10.90. Found C, 65.05; H, 7.61; S, 10.89%. IR ν_{max} (KBr) (cm^{-1}): 3527, (OH), 1282, (SO_2), 1155, (SO_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87–7.93, m, 2H, *o*-C_6H_5; 7.57–7.64, m, 1H, *p*-C_6H_5; 7.48–7.57, m, 2H, *m*-C_6H_5; 3.44, ddd, 1H, $J_{10,9}$ 10, $J_{10,9}$ 6, $J_{10,8}$ 1, H10; 2.61, ddd, 1H, $J_{9,9}$ 13, $J_{9,10}$ 10.5, $J_{9,8}$ 6, H9; 2.30–2.39, m, 1H, H8; 1.60–1.79, m, 2H, H2, H3; 1.39–1.60, m, 8H, H2, H4, 2 × H5, H6, H7, H9; 1.27–1.37, m, 2H, H3, H6; 1.15–1.26, m, 1H, H4; OH not observed. ^{13}C NMR (50 MHz, $CDCl_3$): δ 139.7 *i*-C_6H_5; 133.5 *p*-C_6H_5; 129.1 *m*-C_6H_5; 128.0 *o*-C_6H_5; 78.3 C1; 65.3 C10; 48.1 C8; 35.4 C2; 29.9 C7; 28.3 C6; 24.9 C4; 24.6 C5; 23.7 C3; 22.8 C9. $ESMS^+$: *m/z* 301 (MLi^+, 100), 317 (MNa^+, 100).

(1RS,6SR,8RS)-8-[(4′-Methylphenyl)sulfonyl]bicyclo-[4.2.0]octan-1-ol (6). Anal. Calcd for $C_{15}H_{20}O_3S$: C, 64.25; H, 7.19; S, 11.43. Found C, 64.23; H, 7.22; S, 11.31%. IR ν_{max} (KBr) (cm^{-1}): 3495 (OH), 2924 (CH), 1307 (SO_2), 1148 (SO_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69–7.76, m, 2H, m, *o*-C_6H_4; 7.29–7.35, m, 2H, *m*-C_6H_4; 3.42, dd, 1H, $J_{8\beta,7}$ 8, $J_{8\beta,7}$ 10, H8β; 2.58, ddd, 1H, $J_{2ax,3eq}$ 4, $J_{2ax,3ax}$ 14, $J_{2ax,2eq}$ 16, H2ax; 2.42, s, 3H, CH_3; 2.14–2.25, m, 1H, H6β; 1.96, ddd, 1H, $J_{7,6\beta}$ 11, $J_{7,7}$ 11, $J_{7,8\beta}$ 11Hz, H7, 1.77–1.89, m, 2H, m, H2eq, H7; 1.51–1.66, m, 3H, m, H3, H4, H5; 1.43–1.51, m, 1H, H5; 1.16–1.41, m, 2H, H3, H4. ^{13}C NMR (50 MHz, $CDCl_3$): δ 19.9 C3/C4; 20.2 C7; 21.0 C3/C4; 21.6 C13; 23.1 C5; 30.5 C2; 38.9

C6; 67.2 C8; 76.3 C1; 127.6 C10; 129.7 C11; 137.7 C12; 144.3 C9. ESMS$^+$: *m/z* 303 (MNa^+, 100).

Crystallography

Data collection, structure solution and refinement. Unique data sets for **1**–**6** were measured at 295 K within $2\theta_{max} = 50°$ using a Rigaku AFC7R four-circle diffractometer ($\omega - 2\theta$ scan mode, monochromated Mo Kα radiation, $\lambda = 0.71069$ Å) yielding N independent reflections, N_0 with $I > 2\sigma(I)$ being considered 'observed.' The structures were solved by direct methods and refined by full-matrix least-squares refinement on $|F|$. Positional and anisotropic thermal parameters were refined for non-hydrogen atoms. Positions of hydrogen atoms were geometrically calculated and included in refinement and constrained with estimated isotropic thermal parameters. The hydroxyl hydrogens were located from difference Fourier maps except for **5** and **6**, in which the hydroxyl hydrogen atoms were not included. The Flack parameter for **5** [−0.02(3)] and **6** [−0.13(2)] support the proposed absolute structures. Weights derivative of $w = 1/[\sigma^2(F)]$ were employed. Conventional residuals R, R_w on $|F|$ at convergence are quoted. Neutral atom complex scattering factors were employed, computation used the teXsan crystallographic software package for Windows version 1.06 (Molecular Structure Corporation),[10] ORTEP-3[11] and PLATON.[12]

Crystallographic data for the structural analyses have been deposited with the Cambridge Crystallographic Data Centre, CCDC Nos 176527–176532.

Crystal data. (1*RS*, 5*SR*, 7*SR*)-7-(Phenylsulfonyl)bicyclo[3.2.0]heptan-1-ol (**1**): $C_{13}H_{16}O_3S$, $M = 252.3$, monoclinic, space group $P2_1/c$ (C_{2h}^5 No. 14), $a = 10.538(3)$, $b = 10.148(2)$, $c = 11.840(2)$ Å, $\beta = 98.34(2)°$, $U = 1252.7(4)$ Å^3, $Z = 4$, $D_c = 1.34$ g cm^{-3}, $\mu = 2.52$ cm^{-1}, crystal size $0.60 \times 0.50 \times 0.20$ mm, $N = 2365$, $N_0 = 1803$; $R = 0.045$, $R_w = 0.048$.

(1*RS*, 6*SR*, 8*SR*)-8-(Phenylsulfonyl)bicyclo[4.2.0]-octan-1-ol (**2**): $C_{14}H_{18}O_3S$, $M = 266.4$, monoclinic, space group $P2_1/n$, $a = 16.439(3)$, $b = 5.793(1)$, $c = 15.062(2)$ Å, $\beta = 111.04(1)°$, $U = 1338.8(4)$ Å^3, $Z = 4$, $D_c = 1.32$ g cm^{-3}, $\mu = 2.39$ cm^{-1}, crystal size $0.25 \times 0.25 \times 0.10$ mm, $N = 2607$, $N_0 = 1227$; $R = 0.064$, $R_w = 0.059$.

(1*RS*, 7*SR*, 9*SR*)-9-(Phenylsulfony)bicyclo[5.2.0]-nonan-1-ol (**3**): $C_{15}H_{20}O_3S$, $M = 280.4$, monoclinic, space group $P2_1/n$, $a = 12.032(5)$, $b = 10.385(4)$, $c = 12.640(4)$ Å, $\beta = 111.78(2)°$, $U = 1467(1)$ Å^3, $Z = 4$, $D_c = 1.27$ g cm^{-3}, $\mu = 2.22$ cm^{-1}, crystal size $0.50 \times 0.40 \times 0.10$ mm, $N = 2572$, $N_0 = 1430$; $R = 0.042$, $R_w = 0.045$.

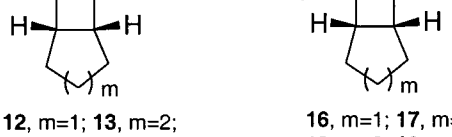
(1*RS*, 8*SR*, 10*SR*)-10-(Phenylsulfonyl)bicyclo[6.2.0]-decan-1-ol (**4**): $C_{16}H_{22}O_3S$, $M = 294.9$, monoclinic, space group $P2_1/c$, $a = 13.289(7)$, $b = 10.275(7)$, $c = 11.539(7)$ Å, $\beta = 104.29(4)°$, $U = 1527(2)$ Å^3, $Z = 4$, $D_c = 1.28$ g cm^{-3}, μ(Mo Kα) = 2.17 cm^{-1}, crystal size $0.50 \times 0.30 \times 0.10$ mm, $N = 2855$, $N_0 = 1213$; $R = 0.055$, $R_w = 0.040$.

(1*RS*, 6*SR*, 8*RS*)-8-(Phenylsulfonyl)bicyclo[4.2.0]octan-1-ol (**5**): $C_{14}H_{18}O_3S$, $M = 266.4$, orthorhombic, space group $P2_12_12_1$ (D_2^3 No. 19), $a = 10.999(1)$, $b = 11.230(2)$, $c = 10.867(2)$ Å, $U = 1342.2(3)$ Å^3, $Z = 4$, $D_c = 1.32$ g cm^{-3}, $\mu = 2.39$ cm^{-1}, crystal size $0.40 \times 0.20 \times 0.10$ mm, $N = 1391$, $N_0 = 886$; $R = 0.043$, $R_w = 0.031$.

(1*RS*, 6*SR*, 8*RS*)-8-[(4′-Methylphenyl)sulfonyl]-bicyclo[4.2.0]octan-1-ol (**6**): $C_{15}H_{20}O_3S$, $M = 280.4$, orthorhombic, space group $P2_12_12_1$, $a = 11.301(4)$, $b = 12.229(7)$, $c = 10.640(6)$ Å, $U = 1470(1)$ Å^3, $Z = 4$, $D_c = 1.27$ g cm^{-3}, $\mu = 2.21$ cm^{-1}, crystal size $0.60 \times 0.40 \times 0.30$ mm, $N = 1525$, $N_0 = 1203$; $R = 0.047$, $R_w = 0.049$.

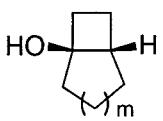
Computational details

Conformational searches of **1a**–**6a** and **7a**–**10a** and **12**–**19** were obtained by Monte Carlo searches in MacroModel v6.0[13] on a Silicon Graphics OCTANE or O2 computer using the MM2* force field and the truncated Newton conjugate gradient (TNCG) minimization algorithm. The searches were performed with 1000 random structures generated per rotatable bond followed by energy minimization and were carried out in a vacuum. For instance, in **6a**, 5000 random structures were minimized. Conformations were kept if their energies were within 25 kJ mol^{-1} above the lowest energy conformation and the conformer populations are reported in the supplementary data (Tables S3–S6), available from the epoc website at http://www.wiley.com/epoc. When comparing conformations, heavy atoms, hydrogen on oxygen and sulfur were used.

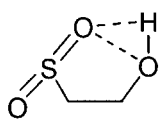


12, m=1; **13**, m=2; **14**, m=3; **15**, m=4

16, m=1; **17**, m=2; **18**, m=3; **19**, m=4



7, m=1; **8**, m=2; **9**, m=3; **10**, m=4



11

RESULTS AND DISCUSSION

Structural results

For all the single-crystal x-ray structures determined in

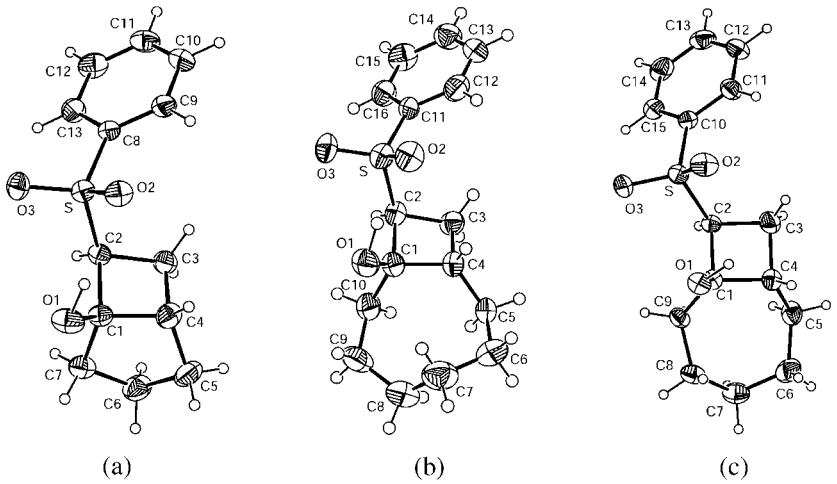


Figure 1. Representation of the molecular structures of (a) 7-(phenylsulfonyl)bicyclo[3.2.0]heptan-1-ol (**1**), (b) 9-(phenylsulfonyl)bicyclo[4.2.0]octan-1-ol (**3**) and (c) 10-(phenylsulfonyl)bicyclo[6.2.0]decan-1-ol (**4**) showing the numbering system. The thermal ellipsoids are drawn at the 30% probability level

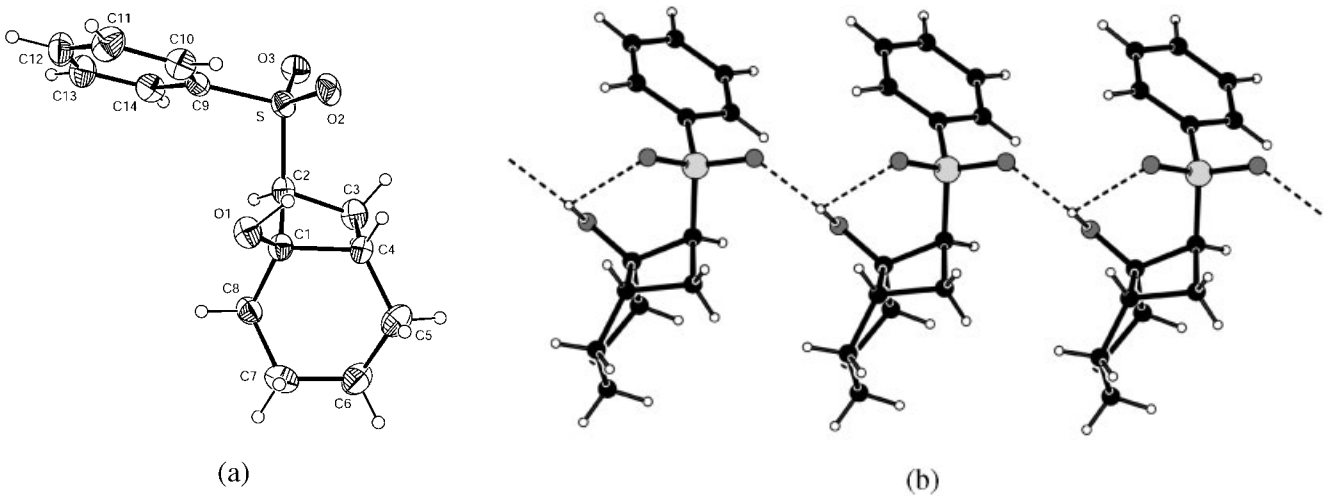


Figure 2. Representation of (a) the molecular structure of 8-(phenylsulfonyl)bicyclo[4.2.0]octan-1-ol (**2**) showing the numbering scheme and (b) the hydrogen bonding scheme for **2**

this study, the asymmetric unit of the unit cell is defined by a discrete single molecule of the compound. The structures of **1**, **3** and **4** show similar relative stereochemistries about the bicyclo[*n*.2.0]alkanol ring with the C2—S bond *cis* to the bridgehead hydroxyl group and *trans* to the fused five-, seven- and eight-membered rings (Fig. 1) (non-IUPAC numbering as displayed in Figs 1–3 is used to facilitate discussion). The phenyl substituent on the sulfur atoms lies approximately parallel with the four-membered ring. The S—O3 bond is directed away from the bicyclo[*n*.2.0]alkanol ring whereas the S—O2 bond is oriented towards this ring, resulting in intramolecular hydrogen bonding interactions with the hydroxyl proton with O1···O2 distances of 2.954(1), 2.972(3) and 2.888(4) Å for **1**, **3** and **4**, respectively. The structure of **2** (Fig. 2) shows the relative stereochemistry of the bicyclo[*n*.2.0]alkanol ring to be similar to that in **1**, **3** and **4**. In **2**, however, rotation of substituents about the C2—S bond results in orientation of the phenyl substituent on the sulfur away from the bicyclo[*n*.2.0]alkanol ring, unlike in **1**, **3** and **4**. This conformer is stabilized by three-centered 'bifurcated' intra- and intermolecular hydrogen bonds[14] between the hydroxyl proton and the sulfone oxygens [Fig. 2(b)] with O1···O2 = 3.184(4) Å and O1···O3^{i} = 2.879(4) Å [symmetry code (*i*) x, $1 + y$, z].

The structures of **5** and **6** compounds differ in a number of significant ways from those of **1**–**4**. Both compounds crystallize with the bridgehead hydroxyl groups *trans* to the C2—S bond (Fig. 3). No intramolecular hydrogen bonding occurs. Rather, intermolecular hydrogen bonds

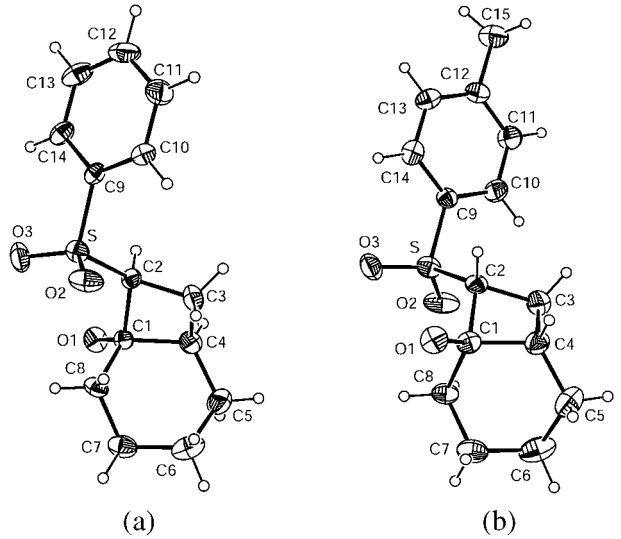


Figure 3. Representation of the molecular structures of (a) 8-(phenylsulfonyl)bicyclo[4.2.0]octan-1-ol (**5**) and (b) 8-[(4′-methylphenyl)sulfonyl]bicyclo[4.2.0]octan-1-ol (**6**) showing the numbering system

form between the hydroxyl protons and O2 of adjacent molecules with O1···O2^{i} (**5**) = 2.798(6) Å and O1···O2^{j} (**6**) = 2.845(4) Å [symmetry codes (*i*) $1/2 + x$, $3/2 - y$, $1 - z$; (*j*) $1/2 + x$, $-1/2 - y$, $1 - z$].

In **1**, the five-membered ring displays a pseudo-'half-chair'[15] conformation with a minor distortion from planarity for a plane through C4—C1—C7—C6. The six-membered rings of **2**, **5** and **6** have a plane through C1—C8—C6—C5 again with a slight distortion from planarity which is reflected by the pseudo-chair conformation of the six-membered ring. In the seven-membered ring of **3** the ring adopts a pseudo-'twist-chair'[16] conformation. The plane through C5—C6—C8—C9 shows a minor distortion from planarity but in the plane through C1—C4—C5—C9 the distortion is more pronounced. In the eight-membered ring of **4** the ring adopts a pseudo-'chair-boat'[17] conformation. The plane of C1—C10—C7—C8 in the 'chair' shows a minor deviation from planarity but the plane of C1—C4—C6—C7 in the 'boat' shows a significant deviation from planarity.

Relevant geometric parameters for these compounds are listed in Tables 1–3. The geometry of the phenylsulfonyl substituent is typical with bond lengths of 1.440(2)–1.454(3) Å for S—O and 1.762(4)–1.784(6) Å for S—C. The bond angles are 117.7(1)–118.5(3)° for O2—S—O3, 106.6(3)–110.8(3) ° for O—S—C and 104.1(3)–105.9(3)° for C2—S—C$_{ipso}$. The C1—C2 bond lengths in the cyclobutanol ring are observed to be of the order of 0.02–0.03 Å longer than the other C—C bond lengths in the four-membered ring, which are, in turn, about 0.02 Å longer than the C—C bond lengths in the five-, six-, seven- and eight-membered ring systems.

The presence of the hydroxyl group on C1 results in distortion of the angular geometry about C1 with values of O1—C1—C2 of 115.0(3)–119.1(6)°, O1—C1—C4 of 113.5(3)–121.0(3)° and O1—C1—C*x* of 106.7(3)–108.8(5)°, with no obvious trends in these angles arising as a result of changes in either ring size or the differences in hydrogen bonding discussed above.

The angular geometries about the bridgehead carbons C1 and C4 show considerable variation across the series of compounds. In the bicyclo[*n*.2.0]alkanol ring of **1**–**4**, the interior angle about C4 (C1—C4—C5) increases with increasing ring size, with values of the order of 108.1(3), 117.3(6), 119.3(3) and 123.7(5)° for the five–eight-membered rings, respectively. The corresponding angles about C1 (C4—C1—C*x*) (*x* = 7–10) show a similar trend with increasing ring size for the five–seven-membered rings, with, however, angles that are about 1–6° smaller than those for C1—C4—C5.

The magnitude of the exterior angles about C1 (C2—C1—C*x*) lies in a relatively narrow range between 110.4(4) and 114.2(3)° with no obvious trends with respect to ring size. By contrast, significant variation is observed in the magnitude of the corresponding angle about C4 (C3—C4—C5). Here the values for the five-, seven- and eight-membered ring compounds **1**, **3** and **4** are of the same order of magnitude as C2—C1—C*x*,

Table 1. Relevant geometric parameters: bond lengths (Å)

	1	**2**	**3**	**4**	**5**	**6**
S—O2	1.443(2)	1.447(5)	1.444(2)	1.454(3)	1.457(4)	1.446(4)
S—O3	1.441(2)	1.432(5)	1.440(2)	1.444(4)	1.441(4)	1.438(4)
S—C2	1.775(3)	1.765(7)	1.763(3)	1.774(5)	1.784(6)	1.757(5)
S—C$_{ipso}$	1.772(3)	1.783(7)	1.762(4)	1.763(5)	1.763(6)	1.768(5)
C1—O1	1.410(3)	1.413(7)	1.424(4)	1.412(6)	1.403(7)	1.415(6)
C1—C2	1.575(4)	1.57(1)	1.571(4)	1.573(7)	1.577(8)	1.578(7)
C2—C3	1.530(4)	1.534(9)	1.534(5)	1.529(7)	1.528(9)	1.525(7)
C3—C4	1.552(4)	1.53(1)	1.539(5)	1.531(7)	1.558(9)	1.532(8)
C1—C4	1.523(4)	1.566(9)	1.549(5)	1.552(7)	1.545(9)	1.542(8)
C1—C*x*[a]	1.528(4)	1.497(9)	1.522(4)	1.532(7)	1.533(8)	1.529(7)
C4—C5	1.512(4)	1.516(9)	1.513(5)	1.512(7)	1.512(9)	1.509(8)

[a] *x* = 7–10 for the five- to eight-membered ring systems, respectively.

Table 2. Relevant geometric parameters: bond angles (°)

	1	2	3	4	5	6
O2—S—O3	117.7(1)	118.2(3)	118.4(2)	117.8(2)	118.2(3)	118.5(3)
O2—S—C2	108.7(1)	110.8(3)	108.6(2)	108.5(2)	109.2(3)	108.4(3)
O2—S—C_{ipso}	107.8(1)	107.2(3)	107.6(2)	107.7(2)	108.1(3)	107.0(2)
O3—S—C2	108.4(1)	107.5(3)	108.9(2)	109.3(2)	107.4(3)	108.4(3)
O3—S—C_{ipso}	108.5(1)	106.6(3)	107.8(2)	108.0(3)	108.8(3)	108.8(3)
C2—S—C_{ipso}	105.1(1)	105.9(3)	104.7(2)	104.8(3)	104.1(3)	104.8(2)
C1—C2—C3	87.9(2)	87.5(6)	90.0(3)	88.5(4)	88.9(5)	87.8(5)
S—C2—C1	113.1(2)	118.9(5)	117.9(2)	114.1(4)	121.1(5)	121.2(4)
S—C2—C3	112.9(2)	111.0(5)	117.9(2)	114.1(4)	120.5(5)	122.4(5)
C2—C3—C4	90.9(2)	90.5(6)	89.9(3)	90.7(4)	87.1(5)	88.6(5)
C1—C4—C3	89.0(2)	87.7(5)	90.6(3)	89.2(4)	89.0(5)	88.8(5)
C1—C4—C5	108.1(3)	117.3(6)	119.3(3)	123.7(5)	118.2(6)	118.6(6)
C3—C4—C5	116.1(3)	122.6(7)	114.6(4)	115.1(5)	123.0(6)	122.3(6)
C2—C1—C4	90.3(2)	87.9(5)	88.2(2)	88.4(4)	85.9(5)	86.3(5)
C4—C1—Cx[a]	105.0(2)	111.7(6)	118.8(3)	116.4(5)	112.2(6)	113.2(5)
C2—C1—Cx[a]	113.0(2)	110.6(6)	114.2(3)	110.1(4)	112.7(5)	114.1(5)
O1—C1—C2	118.3(2)	119.1(6)	115.0(3)	116.8(4)	117.6(5)	117.2(5)
O1—C1—C4	121.0(3)	117.7(6)	113.5(3)	117.9(4)	118.1(6)	117.8(5)
O1—C1—Cx[a]	107.9(3)	108.6(6)	106.7(3)	106.6(4)	108.8(5)	107.4(5)

[a] x = 7–10 for the five- to eight-membered ring systems, respectively.

ranging from 114.6(4) to 116.1(3)°. The values for the six-membered ring complexes **2, 5** and **6**, however, increase by 6–8° to 122.3(6)–123.0(6)°. Examination of the molecular structure of these complexes suggest that the origin of this effect is related primarily to the conformational structure of the rings adjacent to the bond between the bridgehead atoms, C1 and C4. For the five-, seven- and eight-membered ring systems, the C1—Cx and C4—C5 bonds adopt pseudo-eclipsed conformations, with torsion angles C5—C4—C1—Cx increasing in the sequence 6.7(5)° for **3**, −13.4(3)° for **1** and −21.8(8)° for **4**. The four-membered ring shows a similar distortion from planarity with C3—C4—C1—C2: 8.9(3)° for **3**, −10.2(2)° for **1** and −13.5(4)° for **4**. This conformational arrangement is illustrated in Fig. 4(a) for **1**.

For the six-membered ring systems, the pseudo-chair conformational structure necessitates an increase in the C5—C4—C1—Cx torsion angle to values greater than 30° [−33.4(9)° for **2**, 36.9(9)° for **5**, −33.4(8)° for **6**]. A distortion of similar magnitude is not possible for the constrained four-membered ring system where C3—C4—C1—C2 increases only to −18.6(6)° for **2**, 22.3(5)° for **5** and −21.4(5)° for **6**. These differences, illustrated in Fig. 4(b) for **2**, result in the observed differences in the C3—C4—C5 and C2—C1—Cx angles.

Cambridge Structural Database (CSD)

One use of the CSD is to derive molecular dimensions in a very wide range of chemical environments. In this part, we used the CSD first to perform five substructure searches in which a cyclobutanol ring was part of a bicyclo[n.2.0]alkanol (n = 2–6) {CSD refcodes (* indicates displayed intermolecular hydrogen bonding): (bicyclo[3.2.0]heptanols) KOGDUF, LOKZUG, PABWEU, VOXNUR*, YAHXIO*, (bicyclo[4.2.0]octanols) CERVEA, CYBUTB10, FINTEB, FINTIF, LALWIE*, MTCDOL, VOXPAZ*, WAMTEJ*, YAHXIO*, YAVNAK, ZIVSIG, VIVSOM, (bicyclo[5.2.0]nonanols) HALRER*, HALRIV*, LALWOK, TCTDOL*, (bicyclo[6.2.0]decanols) HOXTHD*, YAHXIO*}. No structures were obtained for the bicyclo[2.2.0]hexan-1-ol substructure search. The other substructure searches gave structures that were polycyclic and we therefore focused

Table 3. Relevant geometric parameters: torsion angles (°)

	1	2	3	4	5	6
S—C2—C1—O1	22.4(3)	26.9(9)	−15.6(4)	18.4(6)	92.1(6)	−91.8(6)
O2—S—C2—C3	−52.7(2)	−57.7(6)	−43.6(3)	−55.5(5)	−30.6(6)	34.4(6)
O2—S—C_{ipso}—C_{or}	18.3(3)	−6.2(7)	27.3(3)	17.2(5)	37.5(6)	−42.4(5)
O3—S—C_{ipso}—$C_{or'}$	−33.0(3)	47.4(7)	−24.0(4)	−36.7(5)	−14.5(5)	10.7(5)
C3—C4—C1—C2	−10.2(2)	−18.8(6)	8.9(3)	−13.5(4)	22.3(5)	−21.4(5)
C5—C4—C1—Cx	−13.4(3)	−33.4(9)	6.7(5)	−21.8(8)	36.9(9)	−33.4(8)

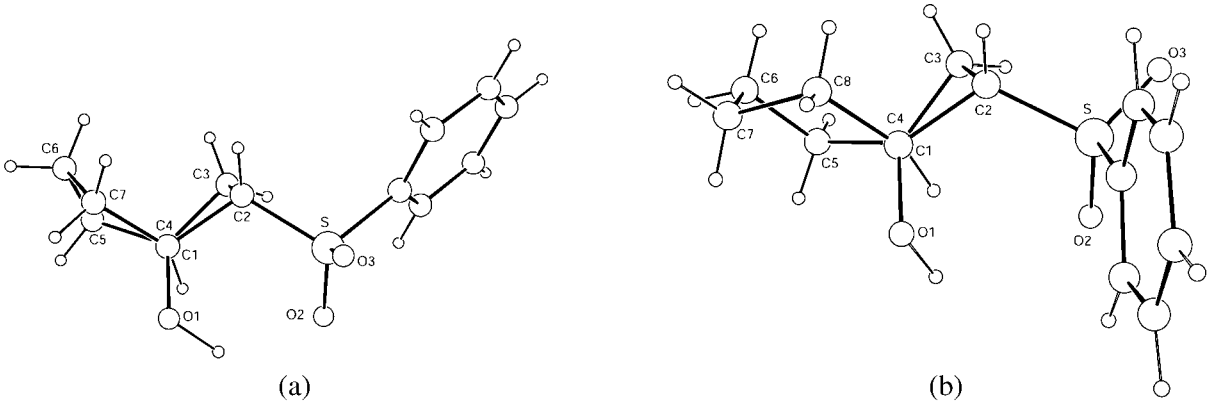


Figure 4. Representation of the molecular structures of (a) 7-(phenylsulfonyl)bicyclo[3.2.0]heptan-1-ol (**1**) and (b) 8-(phenylsulfonyl)bicyclo[4.2.0]octan-1-ol (**2**) illustrating the cyclotorsion of the ring systems adjacent to the bond between the bridgehead atoms C1 and C4

our efforts on the cyclobutanol ring and surveyed the known values for bond lengths, bond angles and torsion angles of cyclobutanols within the remaining four substructures. Cyclobutanols in simple fused systems such as those represented in **1–6** were notably absent. Second, we used the CSD to derive standard values for the OH bonding in β-hydroxy sulfones and the bicyclo-[*n*.2.0]alkanol substructures [CSD refcodes (* indicates displayed intramolecular hydrogen bonding): GOKNAV, HABWOW, HAGCEX, HAXNUP*, JAHKAE, JAHKIM*, JIBNEN*, JUMWIX*, JUMWIX10*, KOGDUF, NEXVIV*, NIRSEM*, NOBWEG, QAJTIE, SOKDUR*, TAPCOC, TASLUU*, WIRYOL*, WOTGER*, XAYSEV, YEGLIF*, ZUCMIT*]. All crystallographic data were retrieved from the Version 5.22, October 2001 (245 392 entries) release of the CSD.[18] Searches for bicyclo[*n*.2.0]alkanol substructures **7–10** and β-hydroxy sulfone substructure **11** and intra- and intermolecular non-bonded OH···O and O···O contacts within these substructures were carried out using the program QUEST. Data analyses were performed with VISTA. [Substructures were only located in entries that (a) were organic compounds within CSD chemical classes definitions, (b) had error-free coordinate sets in CSD check procedures, (c) exhibited no crystallographic disorder, (d) contained no polymeric connections and (e) had a crystallographic *R* factor $\leq$0.10. In addition, for non-bonded contact searches entries had the further constraints of (f) that connectivities were perfectly matched and (g) that the atom coordinates field was present. All H atoms involved in non-bonded contact searches were placed in normalized positions, i.e. they were repositioned along their x-ray determined O—H vectors at a distance from O equal to the appropriate mean bond length established from neutron studies[19] with the condition OH···O distances $<$2.1 Å (sum of van der Waals radii with 1.20 Å for H and 1.52 Å for O).[20] Intramolecular non-bonded contacts of S═O···HO were limited to a minimum and maximum S-PATH of 5.] In the bicyclo[*n*.2.0]alkanol substructure **7–10** searches only structures with a *cis* fused bicycloalkanol ring were used in obtaining values. In the β-hydroxy sulfone substructure **11** search structures where the sulfonyl group was part of a ring or a SO_3^- group or adjacent to a heteroatom such as O or N were excluded.

The notable trends observed of the x-ray data for the simple fused systems **1–4** on direct comparison with the range of values obtained from the CSD substructure series **7–10** were that in the x-ray data, (i) the four-membered ring bond angles of **1–4** varied by 1.29–3.27° and were closer to 90° by comparison with the maximum range of the CSD substructure series **7–10**; and (ii) the four-membered ring torsion angles of **1–4** varied by 3.3–7.6° less than the maximum torsion observed in the CSD substructure series **7–10**. These variations are a reflection of the lack of conformational strain imposed by further cyclic rings as observed in the polycyclic rings of the CSD substructure series **7–10**. It can be inferred that the conformation of the cyclobutanol ring within a bicyclo-[*n*.2.0.]alkanol (x-ray crystallography) or other polycyclic structure (CSD) is variant with each molecular structure.

We further explored the presence of hydrogen bonding in the substructures from the CSD. For the CSD bicyclo[*n*.2.0]alkanol substructures **7–10**, only 40% displayed intermolecular hydrogen bonding OH···O of the order 1.725–2.054 Å. For the β-hydroxy sulfone substructure **11**, 60% displayed intermolecular hydrogen bonding between S—O···HO of the order 1.715–2.107 Å. No intramolecular hydrogen bonding was observed in either case. No further analysis was carried out owing to the small numbers of substructures.

Conformational studies

From Monte Carlo conformational searches of compounds **1–6**, the global energy minimized structures **1a–6a**

were obtained and values for bond angles and C3—C4—C2—C1 and C5—C4—C1—C*x* cyclotorsion angles were derived. The presence of intramolecular hydrogen bonding in structures **1a**–**4a** was observed. Further Monte Carlo conformational searches for substructures derived from **1a**–**6a** in which the sulfonyl group or the hydroxyl group was absent or both the sulfonyl and hydroxyl groups were absent gave three subsequent sets of global energy minimized structures **7a**–**10a, 16**–**19** and **12**–**15**, respectively. For structures **12**–**15**, the lowest energy conformation resulted in a planar cyclobutane ring. These were ignored and the first structures containing a non-planar cyclobutane ring were reported (Table S3, supplementary data). In addition, unsubstituted cyclobutane was modeled and values for cyclotorsion of 20.1° and bond angles of 88.2° were obtained.

In this study, a direct angle to angle comparison between the structures **1**–**6** and **1a**–**6a** was carried out and the trends were observed. The bond angles of the four-membered ring of **1**–**6** varied by a maximum angle of 1.8° from the modeling structures **1a**–**6a**. Similar trends for angular geometries about the bridgehead carbons C1 and C4 to those observed in **1**–**6** were seen in structures **1a**–**6a**. Thus, in the bicyclo[*n*.2.0]alkanol ring of **1a**–**6a**, the interior angle about C4 (C1—C4—C5) increases with increasing ring size, with values of the order of 106.1, 117.6, 118.9 and 120.8° for the five–eight-membered rings, respectively. The corresponding angle about C1 (C4—C1—C*x*) shows a similar trend with increasing ring size, with, however, smaller angles of generally up to 2.5° less than those for C1—C4—C5.

The magnitude of the exterior angles about C1 (C2—C1—C*x*) lies in a relatively narrow range between 112.3 and 119.9° with no obvious trends with respect to ring size. By contrast, significant variation is observed in the magnitude of the corresponding angle about C4 (C3—C4—C5). Here the values for the five-, seven- and eight-membered ring compounds **1a**, **3a** and **4a** are of the same order of magnitude as C2—C1—C*x*, (112.4° for **4a**, 114.4 for **3a** to 115.2° for **1a**). The values for the six-membered ring complexes **2a**, **5a** and **6a** are, however, 3.5–6.3° larger, and with little variance in magnitude, (118.2° for **2a**, 118.7° for **5a** and **6a**). It is of interest that the angles O1—C1—C2 and O1—C1—C4 are of the order of 109.9–114.8° while the angle O1—C1—C*x* is likewise of the order of 110.9–112.4°. The distortion of these angles in **1a**–**6a** is typically less than that observed in **1**–**6**.

Similar conformational structure effects are observed in **1a**–**6a** to those observed for the x-ray structures **1**–**6**. For the five-, seven- and eight-membered ring systems, the torsion angles C5—C4—C1—C*x* increase in the sequence −4.8° for **1a**, −16.3° for **3a** and −17.1° for **4a**. The four-membered ring shows a similar distortion from planarity with C3—C4—C1—C2 − 7.6° for **1a**, −15.4° for **3a** and −17.1° for **4a**. For the six-membered ring systems the pseudo-chair conformational structure necessitates an increase in the C5—C4—C1—C*x* torsion angle to values around than 26° (−25.8° for **2a**, −27.0° for **5a**, −27.0° for **6a**). A distortion of similar magnitude is not possible for the four-membered ring system where C3—C4—C1—C2 increase to −20.2° for **2a**, −27.0° for **6a** and −27.1° for **5a**.

In **1a**–**4a**, intramolecular hydrogen bonding is observed. For **5a** and **6a** no hydrogen bonding was observed. Since Monte Carlo conformational searches were performed in vacuum and on isolated structures, only intramolecular hydrogen bonding is possible. This is in contrast to the x-ray structures **1**–**6**, which displayed intramolecular hydrogen bonding for **1**–**4** and intermolecular hydrogen bonding for **2**, **5** and **6**.

The global energy minimized structures **1a**–**6a**, **7a**–**10a**, **12**–**15** and **15**–**19** in which the sulfonyl and hydroxyl substituents are varied were obtained. The general trends observed were that the cyclotorsion of the four-membered ring (C3—C4—C2—C1) was lower in either the structures with a sulfonyl (**16**–**19**) or hydroxyl group (**7a**–**10a**) than the unsubstituted bicycloalkanes **12**–**15**. However, the least cyclotorsion occurred in **1a**–**4a**, in which both the sulfonyl and hydroxyl group are present and intramolecular hydrogen bonding is observed. Reflecting these trends, the bond angles typically deviated least from 90° in **1a**–**6a** and most from 90° in **12**–**15**. The C5—C4—C1—C*x* torsion angles of **7a**–**10a**, **12**–**15** and **16**–**19** show no obvious trends with respect to ring size. However, as with the cyclotorsion of C3—C4—C2—C1 for the four-membered ring, the least cyclotorsion of C5—C4—C1—C*x* occurred in **1a**–**4a**.

In summary, the combination of x-ray data and conformational analysis in the context of the CSD provides a satisfactory method for the study of the structure of bicyclo[*n*.2.0]alkanols ($n = 3$–6) **1**–**6**. The presence of intra- and intermolecular hydrogen bonding varies between the modeled structures **1a**–**6a** and the x-ray structures **1**–**6**. Intramolecular hydrogen bonding was observed for **1**, **3**, **4** and **1a**–**4a** and intermolecular hydrogen bonding for **5** and **6**. Compound **2** is stabilized by three-centered 'bifurcated' intra- and intermolecular hydrogen bonds. Similar conformational structure effects are observed in the modeled structures **1a**–**6a** to those observed for the x-ray structures **1**–**6**. The degree of cyclotorsion of the four- and five-, six-, seven- and eight-membered rings adjacent to the bond between the bridgehead atoms C1 and C4 is reflected in the magnitude about the exterior angles about C1 (C2—C1—C*x*) and C4 (C3—C4—C5). The six-membered ring systems of **2**, **5**, **6**, **2a**, **5a** and **6a** showed noteworthy increases in the C5—C4—C1—C*x* and C3—C4—C1—C2 torsion angles and this was attributed to the conformational constraints of the pseudo-chair conformation of the six-membered ring. The CSD search also inferred that the conformation of the cyclobutanol ring within a bicyclo[*n*.2.0]alkanol (this study) or other polycyclic structure (CSD) is influenced by the total structure of the molecule.

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