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## Conformational Preference of *trans*-3,5-Cyclohexadiene-1,2-diol, a Benzene Metabolite, from Circular Dichroism, Molecular Mechanics and X-Ray Diffraction Study

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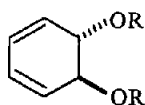
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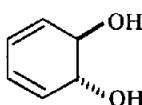
**Abstract.** (S,S)-(+)-3,5-Cyclohexadiene-1,2-diol, (S,S)-1, displays positive  $\pi$ - $\pi^*$  Cotton effect,  $\Delta\epsilon$  +10.0 at 256 nm in methanol. Variable-temperature CD measurements in alcohol solvent indicate that the conformer with equatorial hydroxy groups is more stable than the diaxial one ( $\Delta G^\circ = 0.71$  kcal/mol). The diaxial conformer has one order of magnitude higher rotational strength compared to the diequatorial one, due to the effect of the allylic axial C–O bonds. The diequatorial conformer is stabilized by electrostatic interactions (MMX calculation) and by intramolecular hydrogen bond formation in non-polar solvents. X-ray diffraction study shows that the diequatorial conformer of (S,S)-1 is present in the crystalline state.

### INTRODUCTION

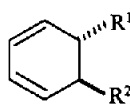
*trans*-3,5-Cyclohexadiene-1,2-diol (*trans*-1,2-dihydroxy-1,2-dihydrobenzene, **1** is one of the initial intermediates in benzene metabolism, formed through the enzyme-catalyzed hydration of benzene oxide<sup>1</sup>. (R,R)-**1** is produced by *in vitro* metabolism of benzene oxide with liver microsomes<sup>2</sup>. Recently there has been growing interest in the use of 3,5-cyclohexadiene-1,2-diols in stereoselective synthesis<sup>3</sup>. Although two chemoenzymatic syntheses of optically active **1** have been reported<sup>4,5</sup> little is known about the stereostructure of **1**. Conformational preference of a 1,3-cyclohexadiene moiety bearing two substituents at stereogenic centers is of particular relevance to the biological activity of benzene metabolites. In addition, an intriguing conformational problem arises when two polar hydroxy substituents are placed onto a cyclohexadiene ring. Previous CD studies showed that for 1,3-cyclohexadiene substituted in the 5-position with methyl (**2a**) or *tert*-butyl (**2b**) the conformer with the equatorial substituent is only slightly favoured over the one with the axial substituent<sup>6</sup>. With two hydroxy substituents of small size, as in **1**, one may expect even further reduction of free energy difference between the diequatorial and diaxial conformers.



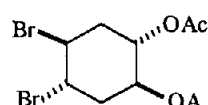
(S,S)-1, R = H  
(S,S)-3, R = Ac



(R,R)-1



**2a**, R<sup>1</sup> = Me, R<sup>2</sup> = H  
**2b**, R<sup>1</sup> = *t*-Bu, R<sup>2</sup> = H  
**2c**, R<sup>1</sup> = R<sup>2</sup> = Me



**4**

In this report we describe the results of the CD study of the optically active (S,S)-1 and its O,O'-diacetyl derivative 3. The solution conformational equilibrium, obtained from the variable-temperature CD measurements, is compared with the results of molecular mechanics (MMX<sup>7</sup>) calculations and with the IR measurements in solution. Furthermore, solid state conformation of (S,S)-1 is determined by the analysis of X-ray diffraction.

## RESULTS AND DISCUSSION

Dienes (S,S)-1 and (S,S)-3 were prepared from optically active dibromide 4 according to published route<sup>5</sup>.

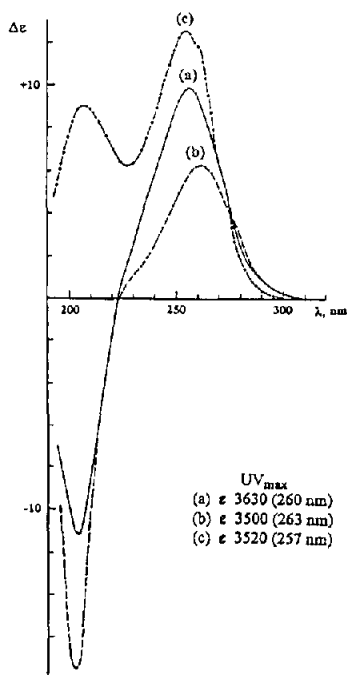


Figure 1. CD spectra of cyclohexadienes recorded at 24°C:  
 (a) (S,S)-1 in methanol,  
 (b) (S,S)-1 in cyclohexane,  
 (c) (S,S)-3 methanol.

The common feature of the CD spectra of dienes (S,S)-1 and (S,S)-3 (Fig. 1) is the appearance of the strong positive Cotton effect,  $\Delta\epsilon +10.0$  (256 nm) and  $\Delta\epsilon +12.6$  (254 nm), accordingly, associated with the lowest energy  $\pi-\pi^*$  transition<sup>8</sup>. This transition is also seen in the UV spectra as a medium intensity band ( $\epsilon$  3500) with  $\lambda_{\text{max}}$  around 260 nm. The Cotton effect of (S,S)-1 at ca. 255 nm is due to contributions of two conformers, the diequatorial one, with M diene helicity (I), and the diaxial one (II) with, P diene helicity (Fig. 2). While the diene chromophore in I and II is inherently dissymmetric, the rotatory power of I and II does not necessarily follows the diene helicity rule<sup>6,9,10</sup>, originally developed by Moscovitz *et al*<sup>11</sup>. Rather it is expected that allylic axial hydroxy groups in II will contribute strongly according to the allylic axial chirality approach of Burgstahler<sup>12</sup> to give net positive Cotton effect.

In order to determine the conformer population and hence the rotatory strength of I and II we have analyzed the variable-temperature CD data (Table 1) applying the free-energy extrapolation method of Moscovitz, Wellman and Djerassi<sup>13</sup>.

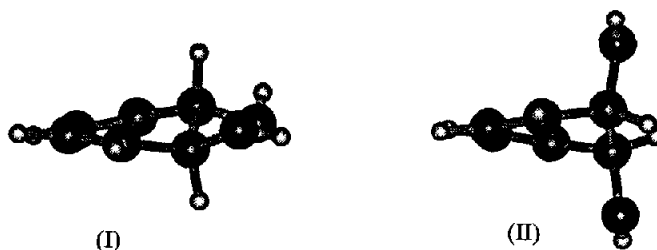


Figure 2. MMX optimized structures of diequatorial (I) and diaxial (II) conformers of (S,S)-1

The diequatorial conformer I was found to be more stable than II in alcohol solvent by  $\Delta G^\circ \approx 0.71$  kcal/mol with the corresponding rotatory strength values,  $R_I = +9.6 \times 10^{-40}$  cgs and  $R_{II} = +101 \times 10^{-40}$  cgs.

T, °C	$\lambda_{\max}$ , nm	$\Delta\epsilon$	$R_r \times 10^{40}$
+24.0	256	+10.0	+30.5
+5.0	256	+9.7	+29.4
-58.5	257	+8.0	+24.3
-88.5	258	+6.7	+21.1
-117.5	260	+5.4	+17.6
-158.0	262	+4.0	+13.6

Table 1. Circular dichroism data for (S,S)-3,5-cyclohexadiene-1,2-diol (1) in ethanol-methanol (4:1), corrected for solvent contraction

It is readily seen that both conformers I and II have positive rotational strength, and the rotational strength of the diaxial conformer II is ca. one order of magnitude higher of the rotational strength of I. High rotational strength of II is primarily due to the presence of two polarizable allylic axial C–O bonds, each constituting part of the C=C–C–O bond system of P helicity. The calculated conformer population in alcohol solvent at 297°K is 77:23 in favor of I. From the data of Fig. 1 it is evident that in nonpolar solvent cyclohexane the I : II ratio is increased to 90:10 due to further stabilization of conformer I by intramolecular hydrogen bond. This results in diminished Cotton effect,  $\Delta\epsilon +6.3$  at 262 nm. The presence of intramolecular hydrogen bond is confirmed by the measurement of concentration - dependent IR spectra in chloroform solution (Fig. 3). At low concentration, 20 mM, peaks due to intramolecular ( $3591\text{ cm}^{-1}$ , strong) and intermolecular ( $3450\text{ cm}^{-1}$ , broad) hydrogen bond are seen. With increased concentration, 200 mM, the intermolecular band at  $3405\text{ cm}^{-1}$  is strengthened. Similar effect is observed for the  $3650\text{--}3700\text{ cm}^{-1}$  band which is presumably due to the free OH group.

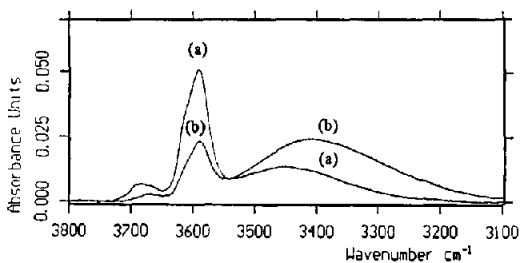


Figure 3. Infrared spectra ( $3100\text{--}3800\text{ cm}^{-1}$ ) of (S,S)-1 in  $\text{CHCl}_3$ :  
(a) 20 mM, 0.25 cm pathlength,  
(b) 200 mM, 0.025 cm pathlength.  
Spectra were recorded at 295 K  
against a  $\text{CHCl}_3$  reference.

The effect of substituent size on the conformation of the cyclohexadiene ring is seen by comparing the lowest energy Cotton effects of (S,S)-1 and (S,S)-3. The more bulky acetoxy substituent in (S,S)-3 appears to favor the axial position in the cyclohexadiene ring, leading to the increase of the positive Cotton effect<sup>14</sup>. Similar behavior of the acetoxy group has been observed in the case of *trans*-9,10-dihydrophenanthrene-9,10-diols<sup>15</sup>.

In order to assess the various factors contributing to the free energy difference between I and II we have carried molecular mechanics (MMX) energy calculation. The minimum energy conformers had C=C-C=C torsional angles -15.9° for I and +15.9° for II and the MMX energy difference was 0.92 kcal/mol in favor of I with intramolecular hydrogen bond. This figure compares rather well with the experimental value 0.71 kcal/mol (*vide supra*) for I without stabilizing effect of the intramolecular hydrogen bond in alcohol solvent. Interestingly, nearly entire energy difference between I and II is due to electrostatic interactions involving the C-O bonds, which are more stabilizing conformer I compared to II. By contrast, MMX calculation of conformational energy of *trans*-1,2-dimethylcyclohexa-3,5-diene (**2c**) points to small energy difference (0.3 kcal/mol) in favor of the *diequatorial* conformer. This difference results from energy differences due to bond angles and torsion angles deformations as well as non-bonded interactions, but not from electrostatic interactions. Calculated C=C-C=C torsional angles in diequatorial and diaxial conformers of **2c** are only slightly larger (0.6°) than those of conformers I and II.

In the crystalline state (S,S)-1 is exclusively present in the diequatorial conformation (I), as shown in Fig. 4. The molecular conformation in the crystalline state agrees with the MMX calculations presented above - the C=C-C=C torsion angle is slightly smaller (-11.5°) than that calculated for an isolated molecule. (see Table 2). The molecules are linked by hydrogen bonds between hydroxyl groups into sheets perpendicular to *z* (Fig. 5). Each hydroxyl group is involved in two hydrogen bonds. The hydrogen bonds can be classified as medium strong - their dimension are listed in Table 2. The H(O1) position suggests its electrostatic interactions with atom O(2). It lies approximately in the molecular plane (Fig. 4), the H(O1)...O(2) distance is 2.70(5)Å; distance O(1)...O(2) is 2.984(4)Å and angle O(1)-H(O1)...O2 is 98(3)°. These dimensions suggest that the interactions between the hydroxyl groups may have a partial hydrogen-bond character. The H(O2) hydrogen atom is directed outside the molecular plane.

Table 2. Bond lengths (Å), valency and torsion angles (°), and the dimensions of hydrogen bonds in the crystal structure of (S,S)-1.

O(1)-C(1)	1.417(5)	O(1)-C(1)-C(6)	108.7(3)	O(1)-C(1)-C(2)-O(2)	73.2(4)
O(2)-C(2)	1.436(4)	O(1)-C(1)-C(2)	111.9(3)	C(6)-C(1)-C(2)-O(2)	-164.1(3)
C(1)-C(6)	1.492(5)	C(6)-C(1)-C(2)	112.6(3)	O(1)-C(1)-C(2)-C(3)	-160.3(3)
C(1)-C(2)	1.518(5)	O(2)-C(2)-C(3)	113.4(3)	C(6)-C(1)-C(2)-C(3)	-37.6(5)
C(2)-C(3)	1.499(6)	O(2)-C(2)-C(1)	109.4(3)	O(2)-C(2)-C(3)-C(4)	151.6(4)
C(3)-C(4)	1.316(6)	C(3)-C(2)-C(1)	111.8(3)	C(1)-C(2)-C(3)-C(4)	27.3(6)
C(4)-C(5)	1.432(7)	C(4)-C(3)-C(2)	121.1(5)	C(2)-C(3)-C(4)-C(5)	-2.5(7)
C(5)-C(6)	1.316(7)	C(3)-C(4)-C(5)	121.5(5)	C(3)-C(4)-C(5)-C(6)	-11.5(7)
O(1)-H(O1)	0.94(5)	C(6)-C(5)-C(4)	120.3(4)	C(4)-C(5)-C(6)-C(1)	-2.4(7)
O(2)-H(O2)	0.90(6)	C(5)-C(6)-C(1)	121.6(4)	O(1)-C(1)-C(6)-C(5)	151.9(4)
		C(1)-O(1)-H(O1)	109(3)	C(2)-C(1)-C(6)-C(5)	27.4(6)
		C(2)-O(2)-H(O2)	107(3)		
Hydrogen bonds:	H(O2)...O(1 <sup>i</sup> )	1.88(6)	O(2)...H(O1 <sup>ii</sup> )	1.79(5)	
	O(2)...O(1 <sup>i</sup> )	2.767(4)	O(2)...O(1 <sup>ii</sup> )	2.695(3)	
	O(2)-H(O2)...O(1 <sup>i</sup> )	169(4)	O(2)...H(O1 <sup>ii</sup> )-O(1 <sup>ii</sup> )	159(5)	

<sup>i</sup>symmetry code: 1+x, y, z. <sup>ii</sup>symmetry code: -x, y-0.5, 1.5-z.

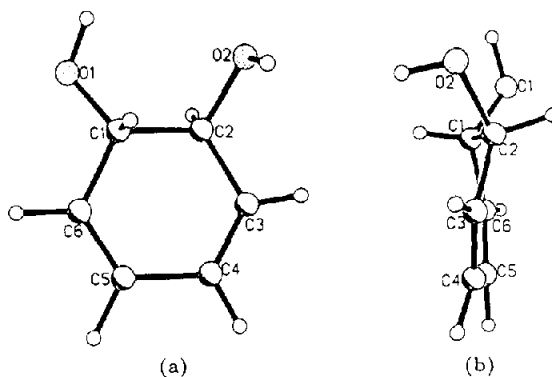


Figure 4. Molecule (S,S)-1 viewed (a) perpendicular to the molecular ring, and (b) approximately down the C(4)-C(5) bond.

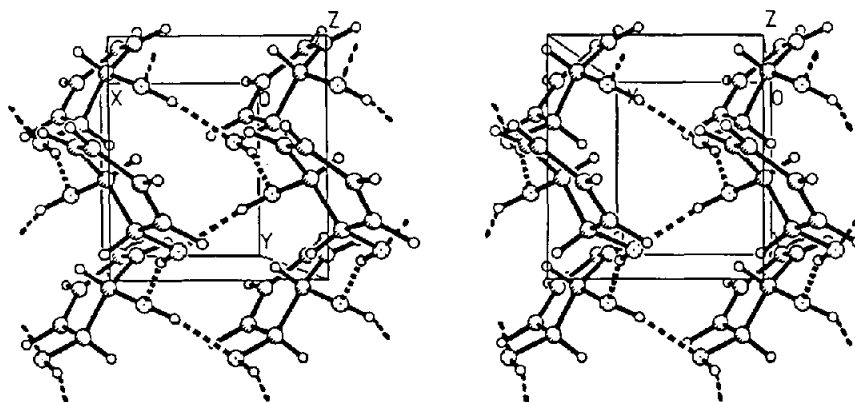


Figure 5. Stereoscopic view of crystal structure (S,S)-1 down axis *z*. Half of the unit-cell contents (one sheet of H-bonded molecules) is included for clarity. Hydrogen bonds are shown by dashed lines.

Similar arrangements of the hydroxyl hydrogen atoms were found in the crystal structure and by the MMX calculations, which suggest a significant contribution of the OH...O intramolecular interactions in stabilizing the diequatorial conformation.

## EXPERIMENTAL

**General Methods.** CD spectra were recorded on a Jobin-Yvon III dichrograph. Low - temperature CD spectra were corrected for solvent contraction<sup>16</sup>. UV spectra was recorded on a Shimadzu UV 160 spectrophotometer. IR spectra were obtained on a Bruker IFS FT-IR spectrometer.

Dienes (S,S)-1 and (S,S)-3 were prepared according to published procedure<sup>5</sup>. (S,S)-1 had m. p. 41-3° (from diethyl ether-hexane),  $[\alpha]_D^{22} + 325.0$  ( $c = 0.75$ , CHCl<sub>3</sub>).

**X-Ray data collection and structure determination.** Crystal data and experimental details of (S,S)-1:  $M_r=112.1$ , orthorhombic, space group  $P2_12_12_1$ ,  $a=4.785(1)$ ,  $b=5.436(1)$ ,  $c=23.003(5)\text{\AA}$ ,  $V=598.3\text{\AA}^3$ ,  $Z=4$ ,  $D_c=1.245\text{g/cm}^3$ ,  $\text{CuK}\alpha$  radiation,  $\lambda=1.54178\text{\AA}$ ,  $\mu(\text{CuK}\alpha)=0.77\text{ mm}^{-1}$ , the final R value is 0.0588 for 826 observed reflections  $I>2\sigma(I)$ .

The sample used for the data collection was a fragment cut off a bigger colourless plate,  $0.5\times 0.2\times 0.1\text{mm}$ . The crystals sublimate and are susceptible to humidity, therefore the sample was phased in a quartz-glass capillary. The measurement was carried out on a KUMA diffractometer in the  $\omega-2\theta$  scan mode at room temperature with a graphite crystal monochromator in the incident beam. Maximum  $2\theta$  was  $142\text{ deg}$  and hkl ranges were: 0/5, 0/6, -28/28, respectively. Of the 1094 unique reflections collected, 826 were considered and observed with  $I>2\sigma(I)$ . The structure was phased by direct methods (SHELXS 86 program<sup>17</sup>) and refined by full matrix least squares using the SHELXL 93<sup>18</sup> program. Anisotropic thermal factors were refined for all non hydrogen atoms. The hydrogen atoms were located on a  $\Delta F$  map and isotropically refined. The positional and thermal parameters have been deposited at the Cambridge Structural Database.

#### REFERENCES AND NOTES

1. Snyder, R.; Longacre, S. L.; Witmer, C. M.; Docsis, J. J. In *Advances in Experimental Medicine and Biology. Biological Reactive Intermediates - II Chemical Mechanisms and Biological Effects*; Snyder, R., Park, D. V., Kocsis, J. J., Jollow, D. J., Gibson, C. G., Witmer, C. M., Eds; Plenum Press: New York, 1982; Vol. 136A, pp. 245-256.
2. Jerina, D. M.; Ziffer, H.; Daly, J. W. *J. Am. Chem. Soc.* **1970**, *92*, 1056.
3. Review: Carless, H. A. J. *Tetrahedron: Asymmetry* **1992**, *3*, 795.
4. Ganey, M. V.; Padykula, R. E.; Berchtold, G. A.; Braun, A. G. *J. Org. Chem.* **1989**, *54*, 2787.
5. Suemune, H.; Hasegawa, A.; Sakai, K. *Tetrahedron: Asymmetry* **1995**, *6*, 55.
6. Lightner, D. A.; Bouman, T. D.; Gawronski, J. K.; Gawronska, K.; Chappuis, J. L.; Crist, B. V.; Hansen, A. E. *J. Am. Chem. Soc.* **1981**, *103*, 5314.
7. MMX is included in the PC Model program (version 4.01), available from Serena Software, P. O. Box 3071, Bloomington, IN 47402-3076.
8. Negative Cotton effect,  $\Delta\epsilon$  -7.2 at 258 nm, has been reported for (R,R)-1 of at least 50% e.e. - see ref. 2).
9. Burgstahler, A. W.; Barkhurst, R. C.; Gawronski, J. K., in *Modern Methods of Steroid Analysis*; Heftmann, E. Ed.; Academic Press: New York, 1973; pp. 349-379.
10. Gawronski, J. K.; Walborsky, H. M. Diene Chirality. In *Circular Dichroism - Principles and Applications*; Nakanishi, K.; Berova, N.; Woody, R. W. Eds.; Verlag Chemie: New York, 1994; pp. 301-334.
11. Moscovitz, A.; Charney, E.; Weiss, U.; Ziffer, H. *J. Am. Chem. Soc.* **1961**, *83*, 4661.
12. Burgstahler, A. W.; Barkhurst, R. C. *J. Am. Chem. Soc.* **1970**, *92*, 7601.
13. Moscovitz, A.; Wellman, K.; Djerassi, C. *J. Am. Chem. Soc.* **1963**, *85*, 3515.
14. Positive Cotton effect of (S,S)-3 at 206 nm is apparently due to the  $n-\pi^*$  transition of the acetoxy chromophore. Note negative band at 204 nm due to the diene chromophore in (S,S)-1.
15. (a) Balani, S. K.; Van Bladeren, P. J.; Shirai, N.; Jerina, D. M. *J. Org. Chem.* **1986**, *51*, 1773. (b) Sayer, J. M.; Van Bladeren, P. J.; Yeh, H. J. C.; Jerina, D. M. *ibid.* **1986**, *51*, 452.
16. Korver, O.; Bosma, J. *Anal. Chem.* **1971**, *43*, 1119.
17. Sheldrick, G. M. *Acta Cryst.* **1990**, *A46*, 467.
18. Sheldrick, G. M. *SHELXL 93. Program for the Refinement of Crystal Structures*. University of Göttingen, 1993.

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