

Empirical Relations between Disulfide Bond Lengths, (N or C)-C-S-S Torsion Angles, and Substituents in Aromatic Disulfides. Crystal and Molecular Structure of 3,3'-Dihydroxydi-2-pyridyl Disulfide

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Abstract: In the 21 reported crystal structures of symmetric disulfides whose sulfur atoms are bound to sp^2 carbon atoms, an empirical relationship is found between the S-S bond length and the X-C-S-S, X = C or N, torsion angle. When X-C-S-S is within about 20° of 90° , the average S-S bond length is 2.08 Å (2.059–2.108 Å) in six structures; when X-C-S-S is within about 20° of 0° , S-S averages to 2.03 Å (1.999–2.050 Å) in 15 structures. The C-S-S-C torsion angles are generally within about 20° of 90° in those molecules. In addition, it is noted that the less frequently encountered X-C-S-S angles near 90° occur only when one strongly electron-donating substituent is present in a position β to the disulfide group in each of the R groups of the RSSR molecule, or when both β positions on each R group are substituted, independent of electronegativity. (If an aromatic ring of an R group is bonded to the disulfide group, the nomenclature ortho instead of β is usually used.) A relatively neutral or electron-withdrawing group in only one β position of each R group (or any substituents at any more distant positions) allows the X-C-S-S torsion angles to be near 0° , and the S-S bond, therefore, to be short. This result is supported by the crystal and molecular structure of 3,3'-dihydroxydi-2-pyridyl disulfide, $C_{10}H_8N_2S_2O_2$, which has been determined by single-crystal X-ray diffraction techniques using counter methods, and has been refined by full-matrix least-squares procedures to a final conventional R index of 0.035. The yellow monoclinic crystals form in the space group $P2_1/c$ with $a = 7.165$ (1) Å, $b = 7.656$ (1) Å, $c = 19.517$ (3) Å, $\beta = 96.77$ (1) $^\circ$, and four molecules per unit cell. The average N-C-S-S torsion angle (9°) indicates that the S-S bond (2.0180 (7) Å) is nearly in the plane of each pyridine ring. The C-S-S-C torsion angle is 93.2° , and the average S-C bond length is 1.782 Å. The empirical rules presented also successfully describe the 11 transition metal ion complexes involving these disulfides whose structures are known. The C-S-S-C torsion angle has a role in governing the S-S bond length, but is important only when X-C-S-S is within about 20° of 90° or when C-S-S-C deviates by about 40° or more from 90° .

Introduction

Various proposals have been offered to account for the variability of the S-S bond length in organic disulfides. Each notes a correlation between this bond length and another structural feature of the disulfide. Hordvik reported a relationship between the S-S bond length and the C-S-S-C torsion angle.¹ Using a selection of more recent results, Shefter noted the lack of such a correlation among some disulfides;² rather, he found the S-S bond length to correlate with another torsion angle, X-C-S-S, where X = C or N. Shefter's result is supported by later work in this laboratory.^{3,4} Table I and Figures 1, 2, and 3 summarize and update previous compilations^{2,4} of *symmetric aromatic* disulfides. An organic disulfide is classified as aromatic if each sulfur atom of the disulfide group is bonded to an sp^2 carbon atom.

Substituents on phenyl rings have been reported to affect the S-S bond length in several diphenyl disulfides. In comparison with diphenyl disulfide,⁵ a longer S-S bond length was found in 2,2'-diaminodiphenyl disulfide,¹¹ but not in 4,4'-dinitrodiphenyl disulfide.⁹ These results might be consistent with a carefully stated theorem that substituents, by their electron-donating ability, increase S-S bond lengths.

The structure of 3,3'-dihydroxydi-2-pyridyl disulfide was investigated, in part, to learn whether a substituent effect is present in the title compound, as compared to its unsubstituted analogue, di-3-pyridyl disulfide.⁴

Experimental Section

3,3'-Dihydroxydi-2-pyridyl disulfide can be prepared by oxidizing 3-hydroxy-2-mercaptopyridine (Aldrich) with hydrogen peroxide. However, single crystals suitable for crystallographic study were obtained by atmospheric oxidation of the thiol in the presence of Fe(II) or Co(II).

A single crystal of $C_{10}H_8N_2S_2O_2$, a parallelepipedon with extreme dimensions $0.18 \times 0.20 \times 0.24$ mm, was selected for X-ray diffraction study and was mounted approximately along its longest dimension.

A Syntex four-circle computer-controlled diffractometer with graphite-monochromatized Mo $K\alpha$ radiation ($K\alpha_1$, λ 0.709 30; $K\alpha_2$, λ 0.713 59 Å) and with a pulse-height analyzer was used for preliminary experiments and for the measurement of diffraction intensities. The space group $P2_1/c$ was assigned on the basis of the systematic absences, l odd for $(h,0,l)$ and k odd for $(0,k,0)$. The cell constants and their standard deviations (Table II) were determined by a least-squares treatment of the angular coordinates of 15 independent reflections with 2θ values up to 25° . The temperature was maintained at 25 (1) $^\circ$ C throughout. The θ - 2θ scan mode was used with a scan rate (ω) in 2θ of 1° min^{-1} . The total background counting time, equal to the scan time, was spent equally at each end of the scan range, which varied from 2.0° at low 2θ to 2.4° at 55° . The data were corrected for minor fluctuations in the check reflections, which were measured after every 100 reflections during the data collection process.

Standard deviations were assigned to the individual reflections according to the formula

$$\sigma(I) = [\omega^2(CT + B_1 + B_2) + (pI)^2]^{1/2}$$

where ω is the scan rate, CT is the total integrated count, B_1 and B_2 are the background counts, and the intensity is $I = \omega(CT - B_1 - B_2)$. A value of 0.02 was assigned to the empirical parameter p ²¹ to account for instrumental inaccuracies. The weights (w) used in least-squares refinement of the structural parameters were the reciprocal squares of $\sigma(F_o)$. Of the 2460 symmetry-independent reflections measured, those for which $2\theta < 55^\circ$, 1968 had intensities larger than three times their standard deviations, and only these were used in subsequent calculations. The intensities were corrected for Lorentz and polarization effects;²² the contribution of the monochromator crystal was calculated assuming it to be half-perfect and half-mosaic in character. An absorption correction ($\mu = 4.64 \text{ cm}^{-1}$)²³ was applied²⁴ which approximated the crystal shape by a $6 \times 6 \times 10$ grid; the calculated transmission coefficients ranged from 0.653 to 0.826. The atomic scattering factors for S⁰, O⁰, N⁰, C⁰, and H (bonded) were used.²⁵ The first was modified to include the real part of the anomalous dispersion correction.²⁶

Structure Determination. The positions of the sulfur atoms could not be readily determined from a three-dimensional Patterson function. Using an overall isotropic thermal parameter ($B_{iso} = 2.2 \text{ \AA}^2$)

Table I. Bond Lengths (Å) and Angles (deg) in Symmetric Aromatic Disulfides^k

compd	S-S	av C-S	av C-S-S	av C-S-S-C	av X-C-S-S	ref
1. diphenyl disulfide	2.023 (1)	1.788 (3)	105.9 (1)	~90	~0	5, 4
2. 2,2'-dicarboxydiphenyl disulfide anion	2.047 (3)	1.790 (7)	106.3 (2)	86.7	15	6, 4
3. 2,2'-dinitrodiphenyl disulfide ^a	2.045 (4)	1.797 (9)	104.4 (3)	85.1	15 (±4)	7, 2
4. 3,3'-dicarboxyl-4,4'-dinitrodiphenyl disulfide ^b	2.023 (2)	1.779 (5)	105.5 (2)	76	16	8
5. 4,4'-dinitrodiphenyl disulfide ^c	2.019 (5)	1.767 (10)	106.2 (3)	72	22	9, 2
6. dipentafluorophenyl disulfide ^d	2.059 (4)	1.770 (7)	101.3 (3)	76.5	~75	10
7. 2,2'-diaminodiphenyl disulfide	2.060 (3)	1.760 (7)	103.3 (3)	90.5	~90	11, 4
8. di-2-pyrimidyl disulfide dihydrate	2.016 (1)	1.781 (2)	104.7 (1)	82.5	4	12, 4
9. 5-[1-(2'-deoxy- α -D-ribofuranosyl)uracilyl] disulfide	2.108 (3)	1.756 (7)	102.0 (2)	50	82 (±6)	13, 2
10. 4-[1-(α -D-ribofuranosyl)uracilyl] disulfide ^e	2.022 (4)	1.79 (2)	104.0 (4)	87	4 (±3)	14
11. 5-(1-methyluracilyl) disulfide ^f	2.074 (3)	1.75 (1)	100.7 (3)	78	83 ± 5	2
12. di-2-pyridyl disulfide	2.016 (2)	1.785 (2)	105.7 (1)	87.1	7	4
13. 3,3'-dihydroxydi-2-pyridyl disulfide	2.0180 (7)	1.782 (2)	104.82 (7)	93.2	10	this work
14. 1,1'-diphenyl-1,1'-dihydroxy-3,3'-dione di-2-butyl disulfide ^g	2.078 (5)	1.756 (8)	103.0 (5)	66.4	~112	15
15. 1,1'-dimethyl-1,1'-dihydroxy-3,3'-dione di-2-butyl disulfide ^h	2.082 (2)	1.744 (5)	103.3 (2)	68.6	100	16
16. formamidinium disulfide dichloride ⁱ	2.017 (2)	1.775 (6)	104.0 (2)	92.3	11	17
17. formamidinium disulfide dibromide	2.044 (10)	1.78 (3)	104.0	89.2	1.6	18, 17
18. formamidinium disulfide diiodide	2.044 (20)	1.75 (4)	98.9	104.8	14.5	18, 17
19. 2,2'-biphenyl disulfide	2.050 (3)	1.75 (1)	98.3 (2)	69	~0	19, 2
20. tetraethylthiuram disulfide ^j	1.999	1.82 (3)	103.5 (3)	90	8 (±1)	20, 2

^a Previously reported with the alternate name bis(*o*-nitrophenyl) disulfide (ref. 7). ^b 5,5'-Dithiobis-2-nitrobenzoic acid (ref 8). ^c Bis(*p*-nitrophenyl) disulfide (ref 9). ^d Bis(pentafluorophenyl) disulfide (ref 10). ^e 4,4'-Di(thiouridine) (ref 14). ^f The disulfide from 1-methyl-5-mercaptopuracil (ref 2). ^g Enol form of 2,2'-dithiobis(1-phenyl-1-3-butanedione) (ref 15). The S and S' positions are interchanged in Table 1 and Figure 1 of ref 15. The four C-C-S-S torsion angles calculated with the correct positions S and S' are S-S'-C(2)-C(3), 120.0°; S-S'-C(2)-C(1), 102.8°; S'-S-C(2')-C(1'), 106.0°; and S'-S-C(2')-C(3'), 119.6°. ^h The enol form of 3,3'-dithiobis(2,4-pentanedione) (ref 16). ⁱ α,α' -Dithiobisformamidinium dichloride (ref 17). ^j Bis(diethylthiocarbonyl) disulfide (ref 20). ^k This tabulation summarizes and updates previous compilations (Shefter, 1970; Raghavan and Seff, 1977).

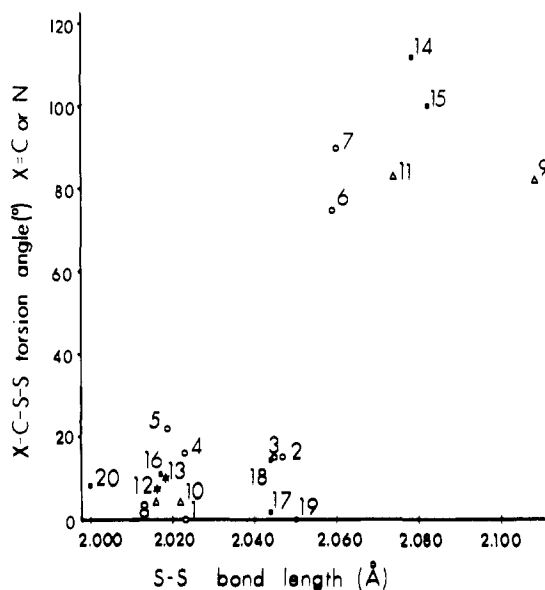


Figure 1. Variation of the S-S bond length with the average X-C-S-S, X = C or N, torsion angle for aromatic disulfides according to their serial numbers as given in Table I: (O) diphenyl disulfide and its substituted analogues; (Δ) di-2-pyrimidyl disulfide and its substituted analogues; (\ast) di-2-pyridyl disulfide and its substituted analogue; (\bullet) others. The concentration of points in the lower left-hand corner represents short S-S bonds in the equatorial conformation. The six points in the upper right-hand region represent the axial conformers and show that their S-S bonds are longer.

estimated from a Wilson plot,²⁷ the normalized structure factor amplitudes of the 160 reflections with $|E| \geq 1.88$ were used in the computer program MULTAN.²⁸ A three-dimensional *E* function, phased as indicated by the solution with the largest CFOM, 2.6, revealed the

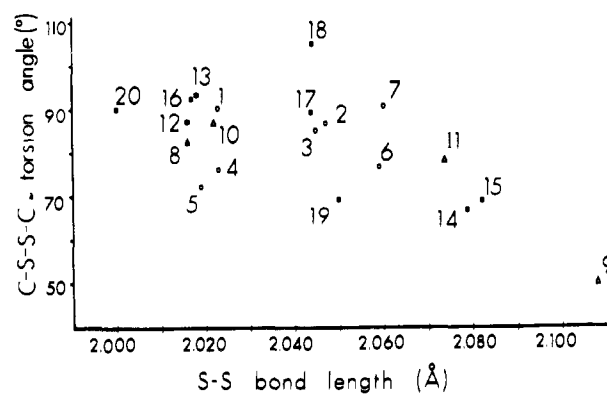


Figure 2. Variation of the S-S bond length with the C-S-S-C torsion angle for aromatic disulfides according to their serial numbers as given in Table I. The symbols have been defined in the previous figure caption.

Table II. Crystal Data

3,3'-dihydroxy-di-2-pyridyl disulfide	C ₁₀ H ₈ N ₂ S ₂ O ₂
monoclinic	mol wt 252.3
space group P2 ₁ /c	Z = 4
a = 7.165 (1) Å	F(000) = 520
b = 7.656 (1) Å	d _x = 1.576 g cm ⁻³
c = 19.517 (3) Å	d _m = 1.567 (2) g cm ⁻³
β = 96.77 (1)°	V = 1063.1 (2) Å ³

positions of all atoms, including the hydrogen atoms. These hydrogen positions were also calculated later, assuming C-H and O-H distances of 0.95 and 0.87 Å, respectively.²⁹ All hydrogen atoms were observed again, more clearly, on an intermediate difference Fourier function.³⁰ Full-matrix least-squares refinement³¹ with anisotropic thermal parameters for nonhydrogen atoms and isotropic thermal parameters

Table III. Fractional Atomic Coordinates and Thermal Parameters with Estimated Standard Deviations (all $\times 10^4$) for Nonhydrogen Atoms^a

atom	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
O(1)	8680 (2)	5049 (2)	5729.0 (7)	151 (3)	139 (3)	12.0 (4)	-20 (5)	-27 (2)	9 (2)
C(2)	8134 (3)	6452 (3)	5334.9 (10)	97 (4)	132 (4)	10.6 (5)	4 (6)	1 (2)	7 (2)
C(3)	8343 (3)	8159 (3)	5544.0 (12)	163 (5)	151 (4)	15.1 (6)	-8 (8)	-15 (3)	-13 (3)
C(4)	7719 (4)	9478 (4)	5091.2 (13)	234 (6)	122 (5)	23.0 (7)	15 (9)	-5 (3)	-9 (3)
C(5)	6898 (4)	9038 (3)	4444.3 (12)	212 (6)	136 (5)	18.5 (6)	68 (8)	-0 (3)	22 (3)
N(6)	6661 (3)	7382 (3)	4227.2 (9)	143 (4)	143 (4)	11.7 (4)	33 (6)	-4 (2)	12 (2)
C(7)	7246 (3)	6120 (3)	4666.8 (9)	92 (4)	125 (4)	10.5 (5)	1 (6)	6 (2)	-2 (2)
S(8)	6933.5 (7)	3867.6 (7)	4462.4 (2)	146 (1)	126 (1)	10.3 (1)	-21 (2)	-4.2 (6)	-0.5 (6)
S(9)	5415.7 (7)	3816.4 (8)	3523.5 (2)	109 (1)	197 (1)	11.5 (1)	-31 (2)	-3.0 (6)	-21.7 (7)
C(10)	7133 (3)	3696 (3)	2932.3 (10)	121 (4)	116 (4)	11.2 (5)	5 (7)	-2 (2)	-7 (2)
N(11)	8946 (2)	3999 (2)	3118.4 (8)	115 (3)	156 (4)	12.2 (4)	-20 (6)	-8 (2)	-6 (2)
C(12)	10127 (3)	3833 (3)	2637.8 (12)	115 (4)	200 (5)	18.3 (6)	-20 (8)	-1 (3)	-7 (3)
C(13)	9546 (3)	3371 (4)	1966.0 (12)	150 (5)	204 (5)	16.5 (6)	9 (8)	31 (3)	-7 (3)
C(14)	7639 (3)	3054 (3)	1775.2 (11)	172 (5)	174 (5)	12.1 (5)	4 (8)	2 (3)	-19 (3)
C(15)	6417 (3)	3230 (3)	2256.4 (10)	126 (4)	136 (4)	12.4 (5)	-1 (7)	-11 (2)	-11 (2)
O(16)	4536 (2)	2971 (3)	2138.8 (8)	118 (3)	272 (4)	13.3 (4)	-51 (6)	-13 (2)	-44 (2)

^a The esd is in the units of the least significant digit for the corresponding parameter. The temperature factor is $\exp[-(h^2\beta_{11} + k^2\beta_{22} + l^2\beta_{33} + hk\beta_{12} + hl\beta_{13} + kl\beta_{23})]$.

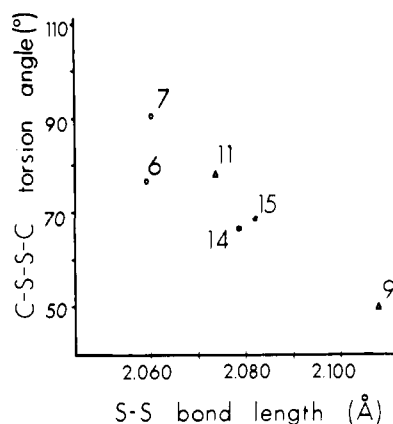


Figure 3. Variation of the S-S bond length with the C-S-S-C torsion angle for the aromatic disulfides in the axial conformation according to their serial numbers as given in Table I. The symbols have been defined in the caption to Figure 1.

for hydrogen atoms led to the final error indices, $R_1 = (\sum |F_o - |F_c||) / \sum F_o = 0.035$ and $R_2 = [\sum w(F_o - |F_c|)^2 / \sum w F_o^2]^{1/2} = 0.041$. The "goodness of fit", $[\sum w(F_o - |F_c|)^2 / (m - s)]^{1/2}$, is 2.42. The number of observations used in least-squares is m (1966), and s (177) is the total number of parameters; the overdetermination ratio (m/s) is therefore 11.1. In the final cycle of full-matrix least squares, the largest shift in a nonhydrogen parameter was less than 3% of its corresponding esd; for the hydrogen atoms, this value was 6%. The only significant peak on the final difference Fourier function, whose esd is $0.07 \text{ e } \text{Å}^{-3}$, was $0.5 \text{ e } \text{Å}^{-3}$ in height and was located approximately midway between S(8) and C(7). Two reflections (2,0,2) (very intense) and (6,2,11), were removed from the final cycles of least-squares refinement because they suffered from obvious errors in measurement. The positional and thermal parameters of the nonhydrogen atoms are given in Table III, and those for the hydrogen atoms are in Table IV. Supplementary Table I of the microfilm edition of this journal is a listing of observed and calculated structure factors.

Discussion of the Structure of the Title Compound

The structure of 3,3'-dihydroxydi-2-pyridyl disulfide is shown in Figure 4. The S-S bond length is $2.0180(7) \text{ Å}$, in close agreement with the $2.016(2) \text{ Å}$ distance found in its unsubstituted analogue, di-2-pyridyl disulfide.⁴ In both of these compounds, the X-C-S-S torsion angles, X = C or N, are near 0 or 180° (see Table V) which indicate that each S-S bond lies approximately in the plane of each pyridine ring. Supplementary Table II of the microfilm edition of this journal gives

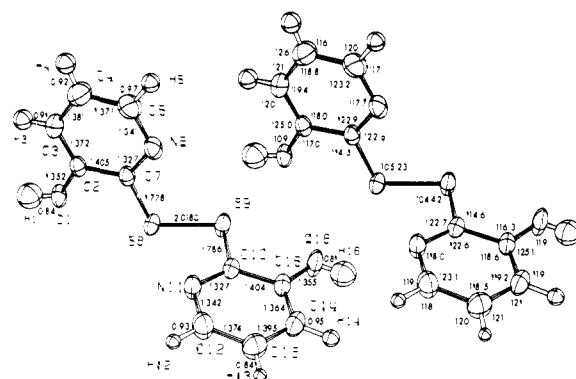


Figure 4. The 3,3'-dihydroxydi-2-pyridyl disulfide molecule is equatorial. Ellipsoids of 50% probability are used.³² The esds are as follows: S-S, 0.0007 Å ; S-C, 0.002 Å ; C-C and C-N, $0.003\text{--}0.004 \text{ Å}$; angles at S, 0.07° ; other angles not involving H atoms, $0.1\text{--}0.2^\circ$; angles involving H atoms, $1\text{--}2^\circ$.

Table IV. Fractional Atomic Coordinates ($\times 10^3$) and Isotropic Thermal Parameters (Å^2) for Hydrogen Atoms^a

atom	x	y	z	B
H(1)	957 (5)	534 (5)	602 (2)	4.4 (9)
H(3)	891 (4)	840 (4)	597 (1)	2.4 (6)
H(4)	782 (4)	1066 (4)	518 (1)	2.3 (6)
H(5)	643 (3)	995 (4)	412 (1)	1.9 (6)
H(12)	1141 (4)	402 (3)	276 (1)	1.1 (5)
H(13)	1035 (3)	317 (3)	169 (1)	0.8 (5)
H(14)	719 (3)	266 (3)	133 (1)	1.5 (5)
H(16)	410 (4)	259 (5)	177 (2)	3.9 (8)

^a The esd is in the units of the least significant digit given for the corresponding parameter.

the results of least-squares plane calculations for the two pyridine rings. The deviation of each C, N, or O atom from its pyridine plane is less than 0.01 Å .

Using the semiquantitative CNDO/2 method, with empirical confirmation from dipole moment and variable temperature ^1H NMR results, Pappalardo and Tondello reported³³ that the X-C-S-S torsion angles are 0 or 180° in the three lowest energy conformations of di-2-pyridyl disulfide. The nitrogen atoms are in the cis,cis, cis,trans, or trans,trans positions with respect to the S-S group. Of the three conformations, the cis,cis was lowest in energy by a small amount.

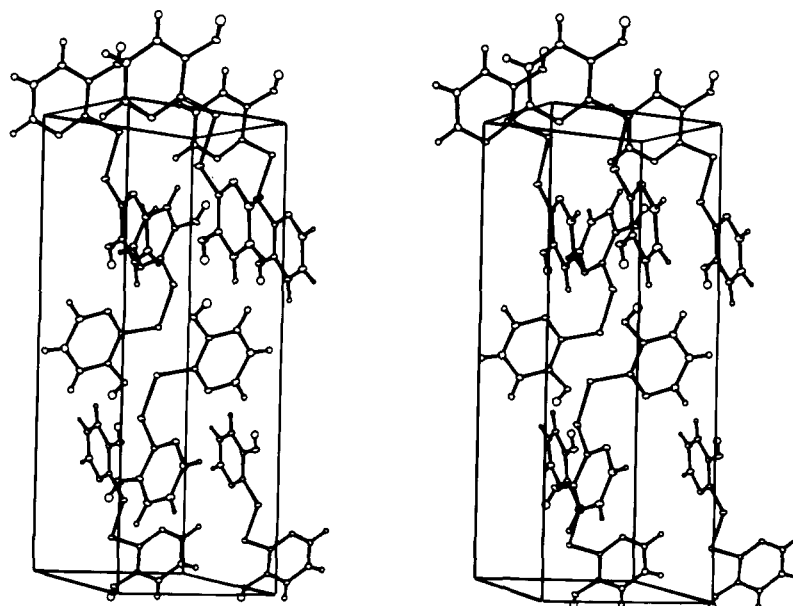


Figure 5. Stereoview of the crystal structure of 3,3'-dihydroxydi-2-pyridyl disulfide in its unit cell, showing ellipsoids of 10% probability.³² The view is approximately into $+a$, with b horizontal and c vertical in the plane of the page.

Table V. Selected Torsion Angles (deg)

atoms	angle
C(7)-S(8)-S(9)-C(10)	93.16
N(6)-C(7)-S(8)-S(9)	4.5
N(11)-C(10)-S(9)-S(8)	13.6
C(2)-C(7)-S(8)-S(9)	174.5
C(15)-C(10)-S(9)-S(8)	165.5
N(6)-C(7)-C(2)-C(3)	2.1
N(11)-C(10)-C(15)-C(14)	1.2

This particular conformation was the only one not observed in the crystal structure of di-2-pyridyl disulfide.⁴

The molecular conformation of a derivative, 5,5'-dinitrodi-2-pyridyl disulfide, was also determined in solution by the mean dipole moment method,³⁴ and the *cis,cis* conformer, which by the di-2-pyridyl disulfide calculations should be lowest in energy, was experimentally confirmed.

In the compound reported here, the *cis,cis* conformation is again observed. However, the other two conformers would have one or two close sulfur-hydroxyl contacts and are severely disfavored for this steric reason.

The corresponding bond parameters of the two pyridine rings agree very well and are in close agreement with those observed in 2,2'-bipyridine,^{35,36} 6-chloro-2-hydroxypyridine,³⁷ and 2,3,5,6-tetrachloro-4-hydroxypyridine.³⁸ With the exception of two longer bonds, C(2)-C(7) = 1.405 (3) Å and C(10)-C(15) = 1.404 (3) Å, the remainder of the pyridyl group compares favorably with that observed in the ordered pyridyl ring of di-2-pyridyl disulfide.⁴ In the latter compound, the corresponding value was C(6)-C(5) = 1.370 Å. This difference in C-C bond length is apparently due to the presence of the hydroxyl groups.

The average C-S bond length of 1.782 (2) Å and the C-S-S bond angles (105.23 (7) and 104.42 (7)°) compare favorably with the corresponding values observed in the other aromatic disulfides presented in Table I. The torsion angle C(7)-S(8)-S(9)-C(10) is 93.2°; in unconstrained disulfides, the C-S-S-C torsion angle is usually found to be within 10° of 90° (see Figure 2). The angle between the two pyridyl rings is 89.7°.

The shortest intermolecular distances are listed in Supple-

mentary Table I11 of the microfilm edition of this journal. Hydrogen bonding occurs between N(6) and O(16) at a distance of 2.74 Å (O(16)-H(16)⋯N(6) = 162°); see Figure 5. N(11) and O(1) do not participate in hydrogen bonding.

Empirical Relationships

Shefter classified aromatic disulfides² as one of two possible conformers according to the X-C-S-S torsion angle, where X = C or N. The title compound, with N-C-S-S torsion angles near 0° (see Figure 4), has the equatorial conformation. In the less frequently encountered axial conformation, the X-C-S-S torsion angles are near 90°.

In those symmetric aromatic uncomplexed disulfides whose crystal structures have been determined, a correlation, which was noted before,²⁻⁴ can be seen in Figure 1 and Table I. When the X-C-S-S torsion angle is near 0 or 180° (equatorial), the S-S bond length is short (1.999-2.047 Å). When the X-C-S-S torsion angle is near 90° (axial), the S-S bond length is longer (2.059-2.108 Å).

Previous discussions of substituent effects have generally been incomplete and inconsistent. In a search for consistency, the bond parameters of diphenyl disulfide, di-2-pyridyl disulfide, di-2-pyrimidyl disulfide, and their substituted analogues were tabulated and systematically examined. All three of the unsubstituted compounds are equatorial (see Table I). Their ortho-substituted analogues with electron-withdrawing (or electron-neutral or weakly electron-donating) groups, -COO⁻, -NO₂, and -OH (items 2, 3, and 13 in Table I), are also equatorial (see Table VI). On the other hand, their ortho-substituted analogues with strongly electron-donating groups, -NH₂ and =O (items 7, 9, and 11 in Table I), are axial. The only exception to this empirical rule is dipentafluorophenyl disulfide, which, because fluorine is nearly electron neutral, would be expected to be equatorial. This particular compound, however, has substituents in *both* ortho positions of each phenyl ring; for steric reasons, then, the equatorial conformation is severely disfavored. Except for this compound, *all five* axial conformers in Figure 1 (items 7, 9, 11, 14, and 15) have a strongly electron-donating group in an ortho position of each ring or in a β position of each group.

The following empirical rules describe the geometries of aromatic disulfides:

Table VI. Symmetric β -Substituted Aromatic Disulfides

serial no. of compd in Table I	β substituent	Hammett substituent constants ^c	conformation	av C-S
3	-NO ₂	+0.778	equatorial	1.797 (9)
6	-F ^a	+0.062	axial ^a	1.770 (7)
2	-COO ⁻	0.00	equatorial	1.790 (7)
13	-OH	-0.37	equatorial	1.782 (2)
14	=O ^b	-0.52 ^d	axial	1.756 (8)
9	=O	-0.52 ^d	axial	1.756 (7)
11	=O	-0.52 ^d	axial	1.75 (1)
15	=O ^b	-0.52 ^d	axial	1.744 (5)
7	-NH ₂	-0.66	axial	1.76 (1)

^a Both ortho substituents of each phenyl ring are fluorine atoms. ^b -OH and =O occur in the two β positions of each 2-butyl group. ^c In the absence of reliable ortho-substituent data for these aromatic disulfides, the σ -para values were used to imprecisely indicate the electron-withdrawing or electron-donating tendency of these substituents. Reference 39. ^d The value of -O⁻ is given.

(1) In the absence of substituents, the equatorial conformation occurs. As a result, relatively short S-S bonds (2.016–2.023 Å) are found.

(2) One group, not strongly electron donating, at one β position of each R group, allows the disulfide, RSSR, to adopt the equatorial conformation. As a result, short S-S bonds (2.018–2.047 Å) are found. (The withdrawal of electron density from the π system allows the sulfur atom to donate 3p_z lone pair electrons more easily to the π orbital of the unsaturated R group. The favorable overlap of the π orbital of the unsaturated R group and the sulfur 3p_z orbital occurs only in the equatorial conformation.)

(3) One strongly electron-donating group at one β position of each R group leads to the axial conformation. As a result, longer S-S bond lengths (2.060–2.108 Å) are observed. (A strongly electron-donating β substituent releases electron density into the aromatic system. As a result, the axial conformation is required for the avoidance of the unfavorable overlap of the π orbital of the unsaturated R group with the filled sulfur 3p_z orbital.)

(4) Substituents, regardless of electronegativity, in both β positions of each R group require the axial conformation for severe steric reasons, and result in an elongated S-S bond (2.059–2.082 Å).

(5) Substituents more distant from the disulfide group, at γ or δ positions, have no effect on the X-C-S-S torsion angle nor, therefore, on the S-S bond length. (Presumably if these groups were very bulky, X-C-S-S might become axial for steric reasons, and S-S would lengthen.)

For those aromatic disulfides in the equatorial conformation, the S-S bond length does not appear to correlate with the C-S-S-C torsion angle within the quite limited range available (see Figure 2). However, the S-S bond lengths of aromatic disulfides in the axial conformation also depend on the C-S-S-C torsion angles (see Figure 3)—as the C-S-S-C torsion angle deviates from 90°, the S-S bond becomes even longer.

Complexes of Aromatic Disulfides

These aromatic disulfides which remain equatorial or axial (to within 15°) in their complexes with transition metal ions^{3,40,41} show the same relationships between S-S bond lengths and X-C-S-S torsion angles (items 1, 6–9, and 11 in Table VII) as uncomplexed disulfides. Because the coordination of one or more transition metal ions to either sulfur or nitrogen atoms has not required an unusual X-C-S-S angle, the S-S bond is unaffected by complexation. Items 6–9 and

Table VII. Bond Lengths (Å) and Angles (deg) in Transition Metal Ion Complexes of Symmetric Aromatic Disulfides

compd	S-S	av C-S-S-C	av X-C-S-S	ref
1. Fe ^{III} LCI ^a	2.046 (5)	133.6	~80.3	40
2. Ni ^{II} LCIClO ₄ ^b	2.089 (8)	55.4	69.3	42
3. Re ^I LBr ₂ (CO) ₆ ^c	2.140 (9)	116.9	~61.3	43
4. Co ^I LCI ₂ ^d	2.040 (2)	102.2	57	3
5. Cu ^I L ₂ ^{+d}	2.047 (5)	93.3	56	3
6. Hg ^{II} LCI ₂ ^d	2.030 (2)	93.7	14	3
7. Cu ^I L ₂ ^{+d}	2.032 (4)	92.4	12	3
8. Cu ^I _n L _{2n} ^{n+d}	2.025 (4)	81.1	11	3
9. Co ^{II} L(H ₂ O) ₂ (NO ₃) ₂ ^e	2.039 (4)	91.8	9.8	41
10. Cu ^I LCI ^f	2.113 (1)	180.0	3.3	44
11. Cu ^I _n L _{2n} ^{n+d}	2.026 (4)	88.7	2	3

^a The ligand, L, is di[2-[(2-hydroxyphenyl)methylimino]phenyl]disulfide. ^b L = di[2-[(2-pyridylmethyl)imino]phenyl]disulfide. ^c L = diphenyl disulfide. ^d L = di-2-pyridyl disulfide. ^e L = di-4-pyridyl disulfide. ^f L = di-2-pyrimidyl disulfide.

11 in Table VII have X-C-S-S torsion angles near 0°. As a result, short S-S bonds (2.025–2.039 Å) are observed.

Larger deviations of the X-C-S-S angles from 0° (or 180°) or 90° due to chelation have resulted in or contributed to longer S-S bond lengths in four compounds (items 2–5 in Table VII). However, in μ -dibromo- μ -diphenyldisulfido-bis(fac-tricarbonyl)dirhenium(I)⁴³ (item 3), it is the coordination of Re(I) to the disulfide group which is apparently primarily responsible for the very long S-S bond length observed, presumably due to back-bonding. The coordination of a disulfide group to a metal ion which is an unusually good electron donor can result in the elongation of the S-S bond.

The β -substituent effect (vide supra) should operate in chloro[di[2-[(2-hydroxyphenyl)methylimino]phenyl]disulfide]iron(III)⁴⁰ and chloro[di[2-[(2-pyridylmethyl)imino]phenyl]disulfide]nickel(II) perchlorate⁴² (items 1 and 2 in Table VII). Their electron-donating ortho groups (-N=CHC₅H₄N and -N=CHC₆H₄OH) are analogous to the amines in 2,2'-diaminodiphenyl disulfide.¹¹ As compared to the unsubstituted analogue, diphenyl disulfide,⁵ longer S-S bond lengths were found in all three of these ortho-substituted axial conformers.

A uniquely large C-S-S-C torsion angle of exactly 180° was found in chloro(di-2-pyrimidyl disulfide)copper(I) (item 10 in Table VII). In this particular compound, complexation has increased the C-S-S-C torsion angle from 82.5° in the free ligand to 180° in the complex, and this is apparently responsible¹ for the long S-S bond.

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Supplementary Material Available: Observed and calculated structure factors (Table I), least-squares plane calculations (Table II), intermolecular approach distances (Table III) (9 pages). Ordering information is given on any current masthead page.

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C-5 Substituted Pyrimidine Nucleosides. 2. Synthesis via Olefin Coupling to Organopalladium Intermediates Derived from Uridine and 2'-Deoxyuridine

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Abstract: Organopalladium intermediates derived in situ from C-5 mercurated uridine or 2'-deoxyuridine and Li_2PdCl_4 in methanol react with olefins to produce nucleosides substituted at C-5 by carbon chains. 5-Chloromercuriuridine (**1**) reacts with Li_2PdCl_4 and ethylene in methanol to give 5-(1-methoxyethyl)uridine (**4a**), which can be transformed to 5-ethyluridine (**7a**) by catalytic hydrogenolysis. Seven percent deuterium was incorporated into the side chain when the reaction was run in methanol- d_1 , suggesting a mechanism involving a palladium-facilitated hydride shift. 5-Ethyl-2'-deoxyuridine (**7b**) was obtained by the same sequence starting from 5-chloromercuri-2'-deoxyuridine (**2**). The reaction of **2** with Li_2PdCl_4 and propylene in methanol gives three major products, *trans*-5-(1-propenyl)-2'-deoxyuridine (**3b**), 5-(1-methoxypropyl)-2'-deoxyuridine (**4b**), and 5-(1-methoxy-1-methylethyl)-2'-deoxyuridine (**5a**). Styrene and methyl acrylate react with Li_2PdCl_4 and **1** in methanol to give respectively *trans*-5-(2-phenylethenyl)uridine (**3e**) and methyl *trans*-3-(5-uridylyl)propenoate (**3d**). Nucleoside **3d** can also be obtained by the reaction between 5-iodouridine, methyl acrylate, and a catalytic amount of palladium acetate. 5-(4-Hydroxypentyl)uridine (**7d**) and 5-pentyluridine (**7e**) were obtained from **1** and 4-penten-2-ol after palladium-catalyzed coupling and catalytic hydrogenation. 1-Benzyloxy-4-penten-2-ol was employed in a synthesis of 5-(4,5-dihydroxypentyl)-2'-deoxyuridine (**7f**) following a similar procedure.

Introduction

Pyrimidine nucleosides substituted at the C-5 position constitute a class of biologically significant molecules. Within this class one may distinguish three categories. C-5 substituted pyrimidine nucleosides are found as constituents of transfer RNA¹⁻⁴ and DNA.^{1,5-8} Derivatives of 2'-deoxyuridine with C-5 substituents no larger than the *n*-butyl group are of interest as chemotherapeutic agents.⁹⁻¹² Other derivatives have found application in the biochemical and physicochemical study of biological macromolecules.¹³⁻¹⁷ In the search for new nucleoside analogues, antiviral agents, and more sophisticated biological probes, we have sought a new synthetic route to C-5 substituted pyrimidine nucleosides which would allow us to easily attach a wide array of functional groups via carbon chains at C-5. Previous efforts to obtain 5-alkyl-2'-deoxyuridines as antiviral agents illustrate the problems to be expected in any synthesis of a C-5 substituted pyrimidine nu-

cleoside via a route requiring glycosidic bond formation at some stage during the synthesis.^{10,18-23}

We recently reported that pyrimidine nucleosides substituted at C-5 by carbon chains may be readily obtained by the reaction of C-5 mercurated derivatives of uridine and 2'-deoxyuridine^{13,24} with Li_2PdCl_4 and olefins.²⁵ The present paper reports an elaboration of those preliminary results.

Results and Discussion

The reaction of C-5 mercurated nucleosides with Li_2PdCl_4 and monosubstituted olefins in methanol is complicated by a problem which was apparently not encountered in the original studies of Heck.²⁶ In addition to the expected nucleoside substituted olefins, in some instances substantial amounts of C-5 α -methoxyalkyl nucleoside are formed. The major product from reaction of 5-chloromercuriuridine (**1**) with 0.1 M Li_2PdCl_4 and ethylene in methanol was not the expected 5-