tetraol, 13.0 min. The later-eluting tetraol was cochromatographic with the minor tetraol product formed upon osmium tetroxide oxidation of the dihydrodiol. For **2b**, HPLC was run on a Du Pont phenyl column, 4.6 × 250 mm, eluted at 1.2 mL/min with 37% THF in water; detection was at 290 nm. Retention times were as follows: *trans*-**2b** tetraol, 6.5 min; *cis*-**2b** tetraol, 7.8 min; (*p*-nitrophenyl)butanol (internal standard), 8.9 min.

The keto diol product formed from the k_0 reaction of **1a** was identified as follows. Diol epoxide **1a** (ca. 1 mg), in 0.95 mL of dioxane and 0.05 mL of dimethyl sulfoxide, was added to 49 mL of a solution containing 0.1 M sodium perchlorate, 1 mM BES buffer, pH 7, and 8% dioxane. After 24 h, the mixture was acidified to pH ca. 3 with perchloric acid. Excess (ca. 80 mg) solid sodium borohydride was added and the mixture was allowed to stand for 15–20 min. It was then acidified, the products were extracted with ethyl acetate, and the product mixture was subjected to HPLC on a Rainin Microsorb C_{18} column, 10 × 250 mm, equipped with a 50-mm guard column, eluted at 3 mL/min with 40% methanol and 25% acetonitrile in water. Two peaks, t_R 16.7 min (minor) and 23.3 min (major) in a ratio of 1:4.8, which were not present in the mixture prior to borohydride treatment, were collected: m/z (EI) 331, for both products. The major triol was acetylated with acetic anhydride in pyridine, and the acetate was purified by HPLC on a Du Pont Zorbax SIL column, 9.4 × 250 mm, eluted at 10 mL/min with 1.25% methanol and 7.5% ethyl acetate in hexane, t_R 5.7 min. The 300-MHz NMR spectrum in $CDCl_3$ exhibited three singlets corresponding to the methyl protons of a triacetate at δ 2.13, 2.18, and 2.21 ppm; the benzo-ring proton resonances were at δ 3.6 (m, 1 H-1), 4.57 (dd, 1 H-1, J_{gem} 17 Hz, $J_{1,2}$ 5.3 Hz), 5.58–5.68 (overlapping multiplets, H-2 and H-3) and 6.47 (d, H-4, $J_{3,4}$ 7 Hz).

Theoretical Calculations. Ionization energies were calculated by using molecular mechanics to obtain a set of Cartesian coordinates (Bruger, W. XICAMM, a computer-aided molecular modeling system, Version 2.0, Xiris Corp., New Monmouth NJ, 1986) and then by using these coordinates as input to the INDO program (Pople, J. A.; Beveridge, D. L.; Dobosh, P. A. CINDO-INDO Program, Program 141, Quantum Chemistry Program Exchange, Indiana University, 1970) to obtain bonding energies. XICAMM has affinities to mainframe molecular mechanics programs but has modifications to allow running on an IBM PC/AT desk computer and also possesses a convenient graphics interface. CINDO is a FORTRAN program and was run on an IBM-3090 computer.

Registry No. **1a**, 124508-36-7; **1a**·$HClO_4$, 124578-17-2; **1b**, 124508-37-8; **1b**·$HClO_4$, 124578-22-9; **2a**, 124508-38-9; **2a**·$HClO_4$, 124578-18-3; *trans*-**2a** tetraol, 124400-22-2; *cis*-**2a** tetraol, 124508-40-3; **2b**, 114326-34-0; **2b**·$HClO_4$, 124508-35-6; **2c**, 105500-28-5; *trans*-**2c** tetraol, 124508-34-5; MES, 4432-31-9; BES, 10191-18-1; TAPS, 29915-38-6; Tris, 77-86-1; CHES, 103-47-9; CAPS, 1135-40-6; *trans*-3,4-dihydroxy-3,4-dihydrodibenz[*a,j*]acridine, 105467-65-0; *trans*-3,4-dihydroxy-1,2,3,4-tetrahydrodibenz[*a,j*]acridine, 124508-33-4; formic acid, 64-18-6; acetic acid, 64-19-7; benz[*c*]acridine, 225-51-4; *trans*-3,4-dihydroxy-1,2,3,4-tetrahydrodibenz[*c,h*]acridine, 124508-39-0; benz[*a*]acridine, 225-11-6.

X-ray Crystallographic Determination of Absolute Configurations and Conformations of Two Conformational Isomers of 1,2,3,4-Dibenzo-*trans*-6,7-dibromo-1,3-cyclooctadiene, a 2,2′-Bridged Biphenyl

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Abstract: The bridged biphenyl 1,2,3,4-dibenzo-*trans*-6,7-dibromo-1,3-cyclooctadiene (**1b**) exists in four stereoisomeric forms as two interconverting enantiomeric pairs, one with axial (a,a) and one with equatorial (e,e) bromine atoms. The stereoisomers can be separated by chromatography on triacetylcellulose. Crystals of the e,e and a,a forms of the pure enantiomers can be separated manually. The structures and absolute configurations of one of the a,a forms and one of the e,e forms were determined by X-ray crystallography, using the anomalous scattering technique. Both stereoisomers were shown to have the eight-membered ring in the twist-boat–chair conformation, confirming predictions by empirical force-field calculation. Two forms were observed by ^1H and ^{13}C NMR in solution and were shown by analysis of the coupling constants to be the same as in the crystals. The free energy barrier to e,e–a,a exchange was found by NMR band-shape analysis to be 23.9 ± 0.1 kcal/mol at 460–470 K, and by following the change in the CD spectrum to be 22.85 ± 0.05 kcal/mol at 298–303 K.

Stereochemical studies of atropisomeric biaryls have played a leading role in the development of organic stereochemistry.[3] In his pioneering work on the absolute configuration of hindered biaryls, Mislow made extensive use of conformationally restricted 2,2′-bridged biaryls, basing his system of correlations by physical and chemical methods on the results of partial asymmetric reduction of dibenzo- and dinaphthosuberones.[4] In their subsequent studies of ORD and CD spectra of bridged biaryls, Mislow and co-workers[5–9] observed regularities, which permitted determination of absolute configurations from the signs of the rotational strengths

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[3] (a) Christie, G. H.; Kenner, J. *J. Chem. Soc.* **1922**, *121*, 614–620. (b) Shriner, R. L.; Adams, R.; Marvel, C. S. In *Organic Chemistry*; Gilman, H., Ed.; Wiley: New York, 1943; Chapter 4. (c) Turner, E. E. In *Steric Effects in Conjugated Systems*; Gray, G. W., Ed.; Butterworths: London, 1958; Chapter 1. (d) Westheimer, F. In *Steric Effects in Organic Chemistry*; Newman, M. S., Ed.; Wiley: New York, 1956; p 523, and references cited therein.

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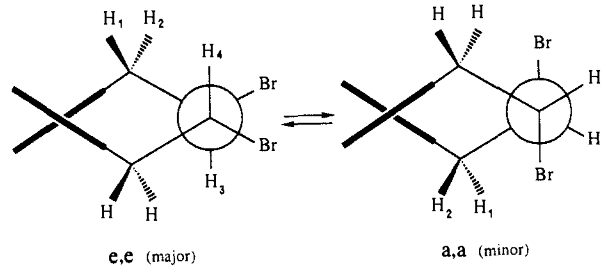
Table I. Experimental Chemical Shifts, Coupling Constants, Calculated Dihedral Angles, and Vicinal Coupling Constants



			H_2			H_3			H_4		
proton	conformation	δ	θ/deg	$^3J_{calc}$/Hz	J_{exp}/Hz	θ/deg	$^3J_{calc}$/Hz	J_{exp}/Hz	θ/deg	$^3J_{calc}$/Hz	J_{exp}/Hz
H_1	e,e	2.97	–	–	−14.2	+171.1[a]	12.1	11.5	–	–	0.0
	a,a	3.18	–	–	−14.2	−77.4	1.0	1.0			
H_2	e,e	3.41				−73.6	1.3	1.6			
	a,a	2.95				+36.2	6.6	6.9	–	–	1.2[b]
H_3	e,e	4.83							+158.3	9.9	9.5
	a,a	4.95							−68.3	1.3	2.0

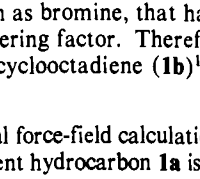
[a] The signs of the angles refer to the E_1 and E_2 forms. [b] Four-bond coupling.

of specific transitions. From this work one important rule was derived for biphenyls, which are restricted by a 2,2′-bridge to a dihedral angle $|\theta| < 90°$ (Figure 1), and which carry no strongly electron-attracting or -donating substituents in the benzene rings: for compounds of this type with the *R* configuration, a positive Cotton effect is invariably observed for the transition, which corresponds to the K band[10] (A band according to Suzuki[11]).

Two of us have recently reported on the enantiomeric resolution of some 2,2′-bridged biphenyls by chromatography on swollen, microcrystalline triacetylcellulose (TAC).[12] These compounds have permitted us to penetrate further into the ultraviolet region of the CD spectrum of the important biphenyl chromophore than was possible for the pioneers in the early 1960s. In connection with the analysis of the spectra, it was considered desirable to perform an experimental determination of the absolute configuration of a suitable compound in the series by using the anomalous scattering technique of X-ray crystallography. The effectiveness of this technique is greatly increased by the presence in the molecule of atoms, such as bromine, that have large anomalous components in the scattering factor. Therefore 1,2,3,4-dibenzo-*trans*-6,7-dibromo-1,3-cyclooctadiene (**1b**)[13] was selected.

Results and Discussion

According to empirical force-field calculations,[12] the most stable conformation of the parent hydrocarbon **1a** is the twist-boat–chair



1 a, R = H
b, R = Br
c, R = CO_2H

(TBC) form with a twist-boat (TB) form 2.8 kcal/mol higher in energy. The corresponding forms of *cis,cis*-1,3-cyclooctadiene were observed by ^1H and ^{13}C NMR by Anet and Yavari,[14] but here the TB form was only 0.5 kcal/mol higher in energy than the TBC form. In the TBC form of **1**, two trans-arranged substituents in positions 6 and 7 may be synclinal (diequatorial, e,e) or antiperiplanar (diaxial, a,a), as clarified by Dvorken et al. for the *trans*-6,7-dicarboxylic acid **1c**.[15]

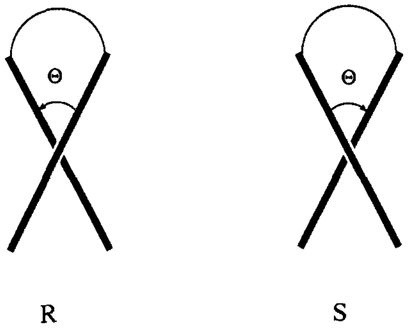


Figure 1. *R* and *S* configurations of 2,2-bridged biphenyl.

Calculations for **1b** with the MMP2-(85) force field[16] predict a major TBC form (a,a) with axial and a minor TBC form (e,e) with equatorial bromine atoms, with the corresponding TB forms ca. 4 kcal/mol higher in energy. ^1H and ^{13}C spectra of **1b** show two sets of resonances in the intensity ratio 63.5:36.5[17] corresponding to two conformers, both with time-averaged C_2 symmetry. Analysis of the 300-MHz ^1H spectrum of the bridge protons of the two forms gave ^3J(H6–H7) = 9.5 Hz for the major and 2.0 Hz for the minor form, in reasonable agreement with values calculated by the method of Haasnoot et al.[18] (Table I) for the e,e and a,a forms, using the geometries from the force-field calculations. Thus, the major form is e,e, contrary to the prediction based on force-field calculations but in agreement with the other coupling constants in the AA′BB′XX′ spin system (Table I).

Exchange broadening was observed at elevated temperatures, and $\Delta G_{471}^{‡}$ (major → minor) = 23.9 ± 0.1 kcal/mol could be derived by spectra simulation (see Experimental Section).

The dibromo compound **1b** contains two stereogenic elements,[19] the CHBr–CHBr (*R,R* or *S,S*) and the biphenyl unit (*R* or *S*) and can consequently form two enantiomeric pairs of diastereomers (*RRR*, *SSS* and *RRS*, *SSR*). Injection of **1b** dissolved in

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Table II. UV and CD Spectra of **1b** in EtOH

	λ/nm (ϵ or $\Delta\epsilon$)
UV	275 (500, sh), 235 (12100), 209.5 (46900)
CD (E_1)[a]	277 (+0.95), 266.5 (+1.26), 235 (+31, sh), 221.5 (+102), 200 (−104)
CD (E_2)[a]	275.5 (−0.21), 267.5 (−0.20), 233.5 (−41.6), 216.5 (−95), 195 (+142, sh)

[a] The CD spectra of E_3 and E_4 are practically mirror images of those of E_2 and E_1, respectively.

Et_2O/EtOH on a column packed with TAC (see Experimental Section) gave on elution with MeOH as the mobile phase at +2 °C four peaks (E_1–E_4) on the chromatogram, with base-line separation between E_1 and E_2 and between E_3 and E_4, but with some overlapping between E_2 and E_3. Equilibration of a sample of pure E_1 at room temperature and reinjection on the TAC column gave peaks corresponding to E_1 and E_2 in the same ratio as in the original chromatogram, i.e., 63.5:36.5, and similarly equilibration of E_4 gave E_3 and E_4 in a 36.5:63.5 ratio.

E_1 and E_2 showed $\alpha_{365} > 0$ and E_3 and $E_4 < 0$. The CD spectrum recorded for E_1 (Table II, Figure 2a) shows positive bands at 235 (shoulder) and 220.5 nm, but that for E_2 (Figure 2b) shows negative bands at 233 and 216.5 nm. Therefore, the positive rotation observed for E_2 at 365 nm was at first unexpected. However, this rotation is weak, and at 303 nm a weak negative rotation was observed. A positive CD band at 195 nm appears as a shoulder on a much stronger positive band at shorter wavelength, and evidently these transitions give contributions that dominate the optical rotation at longer wavelengths.

The CD bands at 235 nm for E_1 and 233.5 nm for E_2 must be ascribed to the A transition, since the corresponding absorption band for **1b** (Figure 2c) and for other dibenzo[*a*,*c*]cyclooctadienes falls in the range 235–238 nm.[20] Thus, the biphenyl unit in E_1 should have the *R* configuration, and since the bromine atoms are equatorial, E_1 must be given the *RRR* configuration. Consequently, E_2 is *RRS*, E_3 is *SSR*, and E_4 is *SSS*.

The rate of equilibration was determined by monitoring the intensity of a strong CD band in solutions of the minor forms (E_2 and E_3) at two different temperatures, giving $\Delta G_{298}^{\ddagger}$ (major → minor) = 22.85 ± 0.05 kcal/mol.

The difference in $\Delta G^{\ddagger}$ from 471 K (NMR) to 298 K (CD), neglecting the difference in solvent, corresponds to $\Delta S^{\ddagger} = -6$ eu, a reasonable value for inversion of a nonionic 2,2′-bridged biphenyl.[20]

When a hexane solution of an equilibrated sample of any one of the pure enantiomers was allowed to evaporate slowly, two types of crystals were formed, one of which can be described as thin, glistening plates and the other as large coarse prisms. Dissolution in $CDCl_3$ and rapid recording of the ^1H NMR spectrum showed the plates to have the diaxial (E_2,E_3) and the coarse prisms the diequatorial conformation (E_1,E_4). One plate-shaped crystal from E_2 and one prism from E_4 were selected for X-ray crystallography.

The unit cell in the crystal of E_2 was found to belong to the chiral space group $C222_1$ and contain two independent molecules, A and B, each of which lies across a 2-fold axis, which passes through the cyclooctadiene ring. The absolute configuration of both kinds of molecules is *RRS*, which confirms the absolute configuration assigned from the CD spectrum. A large number of Friedel pairs of reflections were collected to enable a test of this configuration to be made. Refinement of the *SSR* configuration led to an *R* factor of 0.049, which is considered significantly higher than the *R* factor for *SRR* (0.036). Analysis[21] of 258 Friedel pairs of reflections that were considered to have significant intensities confirmed that the *RRS* configuration was the correct choice. The crystal structure showed both independent molecules in the unit cell to have very similar structures (an iterative least-squares matching to the best fit gave a root mean square

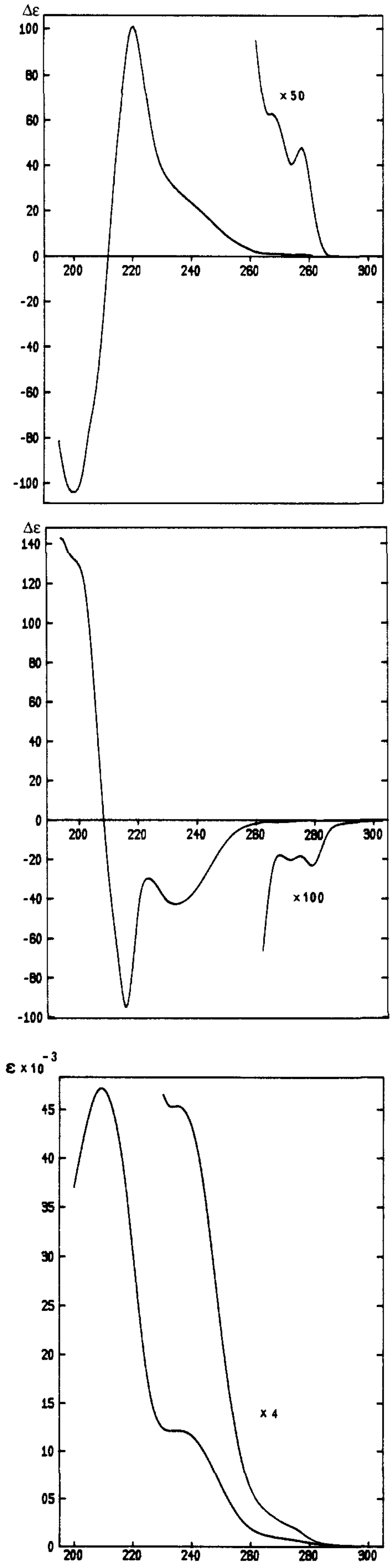

Figure 2. (a, top) CD spectrum of E_1 [e,e (+)] of **1b** in EtOH. (b, middle) CD spectrum of E_2 [a,a (−)] of **1b** in EtOH. (c, bottom) UV spectrum of **1b** in EtOH.

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Table III. Physical Properties and Parameters for Data Collection and Refinement of **1b**, e,e (−) and a,a (+) Forms

	e,e (−)		a,a (+)
formula		$C_{16}H_{14}Br_2$	
molecular weight		366.1	
cryst class	orthorhombic		orthorhombic
space group	$P2_12_12_1$ (No. 19)		$C222_1$ (No. 20)
a, Å	9.002 (3)		10.913 (3)
b, Å	9.566 (2)		9.179 (3)
c, Å	16.587 (4)		27.906 (3)
V, Å^3	1428		2795
Z	4		8
d_{calc}, g/cm	1.702		1.740
$F(000)$	720		1440
λ, Å (Mo K_∞) graphite monochromated		0.70926	
μ, cm^{-1}	59.83		61.20
cryst size, mm	0.35 × 0.45 × 0.70		0.05 × 0.25 × 0.40
temp, °C		18	
take-off angle, deg		6.0	
detector width, mm		variable slit: $4 \times (1.4 + \tan\theta)$	
scan speed, deg/min		variable: 1.6–3.3	
scan type		$\omega/2\theta$	
scan width, deg	$1.0 + 0.35 \tan\theta$		$0.9 + 0.35 \tan\theta$
hkl range	$h, -10 \rightarrow 10$; $k, -1 \rightarrow 11$; $l, -1 \rightarrow 19$ and $h, -10 \rightarrow 10$; $k, -5 \rightarrow 5$; $l, -5 \rightarrow 5$		$h, -13 \rightarrow 13$; $k, -10 \rightarrow 10$; $l, -8 \rightarrow 5$ and $h, -1 \rightarrow 13$; $k, -1 \rightarrow 10$; $l, 6 \rightarrow 33$ (measured only if $h + k = 2n$)
θ range, deg		2–25	
standards (period.) orientation (200 reflcns)	−5,0,10/−1,7,1/6,0,6		4,−2,−18/6,−40/−5,−5,−4
intensity (2 h)	8% loss; corrected		no loss
no. of measd reflcns	4453		4396
no. of unique reflcns	2509		1985
no. of obsd reflcns (NO) [$I > 2\sigma(I)$]	1411		828
no. of variables (NV)	178		178
transmission coeff	0.791–1.476		0.672–1.435
weighting scheme $w = k/[\sigma^2(F) + gF^2]$, k, g	0.081, 0.01244		0.058, 0.0989
highest peak in final diff. Fourier (eÅ^3)	0.58		0.49
agreement factors			
$R = (\sum\|\|F_o\| - \|F_c\|\|)/(\sum\|F_o\|)$	0.0319		0.0357
$R_w = [\sum w(\|\|F_o\| - \|F_c\|\|)^2/(\sum w\|F_o\|)^2]^{1/2}$	0.0334		0.0392
$s = [\sum(\|F_o - F_c\|)^2/(NO - NV)]^{1/2}$	1.68		4.44

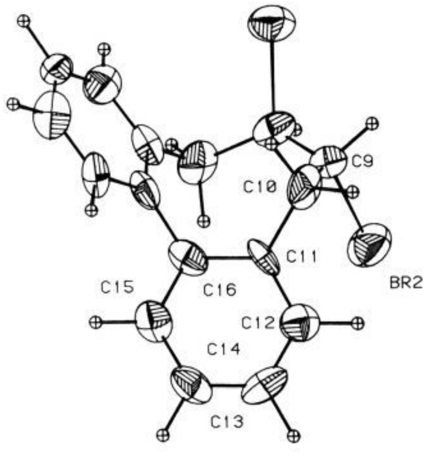

Figure 3. View of the a,a (+) form of **1b** (molecule B).

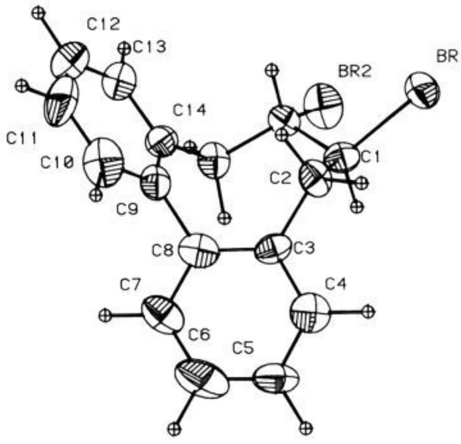

Figure 4. View of the e,e (−) form of **1b**.

distance between the non-hydrogen atoms of 0.11 Å) and to adopt twist-boat–chair conformations with axial C–Br bonds (a,a), thus confirming the deductions from ^{1}H NMR spectra (Figure 3).

The crystal structure determination of the prismatic crystal from E_4 showed the unit cell to belong to the chiral space group $P2_12_12_1$ and the asymmetric unit to contain one complete molecule. The test of the absolute configuration was performed as for the E_2 crystal, and the configuration was found to be *SSS* with a TBC ring and equatorial C–Br bonds (e,e; Figure 4). This result also confirms the conclusion based on CD and ^{1}H NMR spectra. Refinement of the inverse configuration led to an R factor of 0.047, compared with 0.032 for the *SSS* configuration. Analysis[21] of 551 Friedel pairs of reflections confirmed that the *SSS* configuration was correct.

The angle between the least-squares planes through the benzene rings is 62.0° in molecule A and 56.5° in molecule B of the a,a form, and 55.6° in the e,e form. The dihedral angle between the C–Br bonds is 142.4° (A) and 150.0° (B) in a,a, and 66.0° in e,e. The structures of the molecules in the crystals are reasonably well reproduced by the force-field calculations. The mean deviation in the best fit of the calculated a,a form is 0.26 Å for the A molecule and 0.06 Å for the B molecule. The corresponding value is 0.11 Å for the e,e form. The dihedral angles between the C–Br bonds were calculated to 150.2 and 70.9°, respectively.

The biphenyl twist was calculated to be 60.8° for the a,a and 58.7° for the e,e form. It is worth noting that Beaven and Hall,[22] using a geometrical model, calculated this angle to 59° in a related compound, while Dvorken et al.[15] derived a value of 44° based on the UV absorption intensity of the A band.

Conclusion. It has been possible by chromatography and manual separation of crystals to obtain the four possible stereoisomers of the dibenzodibromocyclooctadiene **1b** in pure crystalline form. The X-ray crystallographic study of two of the stereoisomers has provided conclusive determinations of the absolute configurations of two bridged biphenyls and confirmed an earlier rule derived from ORD and CD spectra relating the sign of the rotational strength of the A transition in bridged biphenyls to the sign of the twist angle. In addition, the conformation of the eight-membered ring in **1b** as twist-boat–chair predicted by empirical force-field calculations has been confirmed. The CD spectra of this and related compounds will be discussed in a forthcoming publication.

Experimental Section

Preparation. 1,2,3,4-Dibenzo-*trans*-6,7-dibromo-1,3-cyclooctadiene (1b) was obtained in nearly quantitative yield by addition of 1 mol of bromine to 1,2,3,4-dibenzo-1,3,6-cyclooctatriene in carbon tetrachloride solution,[13] and the compound was purified by chromatography on silica with pentane as the mobile phase to give a colorless solid: MS, 70 eV *m/e* (rel. intensity) 368 (1.8), 366 (3.7), 364 (1.8), 206 (100), 191 (94), 178 (98), 165 (71), 89 (50); ^{1}H NMR data are found in Table I; ^{13}C NMR ($CDCl_3$, 75 MHz) e,e form: 42.44 (CH_2), 60.08 (CH), 127.70 (CH), 128.42 (CH), 128.83 (CH), 130.04 (CH), 136.94, 139.57. a,a form: 33.05 (CH_2), 55.43 (CH), 126.51 (CH), 127.18 (CH), 129.98 (CH), 133.77 (CH), 134.76, 141.20. The last two resonances in each set are from quaternary carbon atoms.

Chromatographic separation of the four stereoisomers of **1b**, E_1–E_4, was performed by using a Conbrio-TAC column[23] packed with swollen, microcrystalline triacetylcellulose.[24] The column was enclosed in a glass mantle, through which cooled ethanol (+2 °C) was circulated. The column was attached to a Varian LDC Model 5000 HPLC instrument, working at 38 atm with MeOH as the liquid phase. The fractions were collected in a cooled receiver on the basis of the trace of the UV detector. Solutions of enantiomerically pure E_1 and E_4 could be obtained directly, and after equilibration of either of them, solutions of pure E_2 and E_3 were obtained in new chromatographic separations.

A solution containing 50 mg of pure E_1 was evaporated, and the residue (an E_1–E_2 equilibrium mixture) was subjected to HPLC (silica, pentane) to remove minor impurities and then dissolved in hexane and allowed to evaporate slowly. Two kinds of crystals (coarse prisms and thin plates) were formed, which could be separated manually. The coarse prisms showed mp 105–106 °C and the plates mp 103–104 °C. Crystals of E_3 and E_4 were obtained in a similar experiment starting from pure E_4.

The CD spectra were recorded with a Jasco Model J-500A spectropolarimeter directly on the MeOH solutions from the chromatographic separations, or on solutions of crystals (E_3 and E_4) in Et_2O/EtOH, and the concentrations were monitored with the UV spectra of the solutions recorded with a Cary Model 2290 spectrophotometer. The CD spectra were recorded at +1 °C by using the thermostating equipment described below.

The first-order rate constant for the e,e → a,a exchange (k_1) was determined by monitoring the intensity of the CD band at 233 nm of a sample of E_2 (or E_3) in a water-jacketed cell connected to a circulation thermostat (Haake Model N3 digital thermostat). k_1 was obtained from the observed rate constant k_{obs} and the equilibrium constant K by using the expressions $k_{obs} = k_1 + k_{-1}$ and $K = k_1/k_{-1} = [a,a]/[e,e]$, where k_{-1} is the rate constant for the reverse reaction. The experiments with E_2 and E_3 gave $k_1 = (1.18 \pm 0.05) \times 10^{-4}\ s^{-1}$ at +25.1 °C and $k_1 = 1.85 \times 10^{-4}\ s^{-1}$ (one experiment) at 30.0 °C, corresponding to $\Delta G^{\ddagger}$ of 22.85 ± 0.05 kcal/mol.

The NMR spectra at ambient temperature were recorded in $CDCl_3$ solution by using a Varian Model XL-300 spectrometer. The ^{1}H spectra of the e,e and a,a forms were analyzed as AA′BB′XX′ systems. Irradiation at either the A or the B position simplified the spectra to AA′(BB′)XX′ type, which were readily analyzed by the iterative technique, yielding $^{3}J_{AX}$, $^{4}J_{AX'}$ (or $^{3}J_{BX}$ and $^{4}J_{BX'}$) and $^{3}J_{XX'}$. J_{AB} could be read directly from the splittings. The results are found in Table I.

Table IV. Fractional Atomic Positional Parameters and Equivalent Isotropic Temperature Factors (Å^2) for the e,e (−) and a,a (+) Forms of **1b** (with esd's in Parentheses) Numbering According to Figures 4 and 3

atom	*x/a*	*y/b*	*z/c*	*U*(iso)[a]
		e,e (−)		
Br1	0.53541 (8)	−0.00347 (10)	0.96805 (5)	0.0516
C1	0.5619 (7)	0.1491 (7)	0.8911 (4)	0.0361
C2	0.6898 (7)	0.1087 (8)	0.8345 (4)	0.0390
C3	0.7650 (5)	0.2303 (7)	0.7916 (3)	0.0342
C4	0.8808 (7)	0.2981 (8)	0.8300 (5)	0.0491
C5	0.9626 (9)	0.4021 (8)	0.7923 (5)	0.0536
C6	0.9300 (8)	0.4343 (10)	0.7132 (6)	0.0632
C7	0.8152 (7)	0.3666 (9)	0.6724 (5)	0.0499
C8	0.7324 (6)	0.2663 (7)	0.7124 (3)	0.0408
C9	0.6036 (7)	0.1994 (7)	0.6684 (4)	0.0367
C10	0.6287 (10)	0.1381 (9)	0.5925 (4)	0.0615
C11	0.5120 (10)	0.0787 (10)	0.5493 (4)	0.0653
C12	0.3748 (10)	0.0814 (9)	0.5800 (5)	0.0654
C13	0.3447 (9)	0.1457 (9)	0.6539 (4)	0.0530
C14	0.4583 (7)	0.2051 (7)	0.6979 (4)	0.0381
C15	0.4204 (6)	0.2735 (8)	0.7768 (3)	0.0378
C16	0.4151 (6)	0.1727 (8)	0.8466 (4)	0.0350
Br2	0.26811 (6)	0.24125 (10)	0.92575 (4)	0.0545
		a,a (+) Molecule A		
Br1	0.55531 (12)	0.37643 (14)	0.43093 (5)	0.0574
C1	0.4995 (9)	0.4157 (10)	0.4969 (4)	0.0319
C2	0.3800 (9)	0.3301 (11)	0.5079 (4)	0.0441
C3	0.2763 (9)	0.3498 (11)	0.4722 (4)	0.0357
C4	0.2687 (10)	0.2532 (13)	0.4357 (5)	0.0476
C5	0.1722 (11)	0.2558 (12)	0.4018 (4)	0.0474
C6	0.0834 (10)	0.3596 (13)	0.4083 (5)	0.0534
C7	0.0865 (10)	0.4571 (13)	0.4460 (5)	0.0475
C8	0.1830 (10)	0.4488 (9)	0.4796 (5)	0.0341
		a,a (+) Molecule B		
Br2	0.41813 (14)	1.14887 (14)	0.32386 (6)	0.0759
C9	0.4341 (11)	1.0948 (12)	0.2550 (4)	0.0528
C10	0.3604 (9)	0.9541 (13)	0.2435 (5)	0.0489
C11	0.3686 (10)	0.8265 (10)	0.2776 (4)	0.0344
C12	0.2869 (12)	0.8133 (14)	0.3157 (5)	0.0541
C13	0.2907 (11)	0.6992 (15)	0.3453 (5)	0.0523
C14	0.3770 (12)	0.5899 (14)	0.3372 (5)	0.0551
C15	0.4557 (11)	0.5991 (11)	0.3001 (5)	0.0473
C16	0.4571 (11)	0.7168 (10)	0.2706 (4)	0.0417

[a] The equivalent isotropic temperature factor $U(iso) = (U_{11} \cdot U_{22} \cdot U_{33})^{1/3}$.

The high-temperature ^{1}H NMR spectra were recorded in $(CCl_3)_2C{=}O$ solution by using a JEOL Model MH-100 spectrometer. The exchange-broadened spectra of the 6,7-protons were simulated as the X,X′ part of an ABXX′ system, using the DNMR5 program.[26] The reduced spectral system was necessitated by the space restrictions of the program, and it was considered permissible since the spectrum was fairly well reproduced in the slow-exchange limit. The determination of the rate constants and T_2 values was performed as described previously.[27] The rate constant to e,e → a,a exchange was estimated to 45 s^{-1} at 186.6 °C and 75 s^{-1} at 198.2 °C, corresponding to $\Delta G^{\ddagger} = 23.8$ and 24.0 kcal/mol.

The empirical force-field calculations were performed with the MM2-(85) force field[16] using the interactive computer graphics program MOLBUILD.[28]

X-ray Crystallographic Procedure. Data Collection: Crystals of suitable sizes were mounted on glass fibers. An Enraf-Nonius CAD4 diffractometer was used to measure the unit cell dimensions and to collect the data. The crystal and data collection parameters are listed in Table III. The unit cell constants were obtained by least-squares analysis of the diffractometer setting angles of 25 well-centered reflections in the range 2 θ = 20–36° for the e,e and 28–34° for the a,a form. The intensities were reduced to a standard scale by routine procedures.[29]

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Lorentz and polarization corrections were applied and absorption corrections[30] were performed. Scattering factors for neutral atoms were taken from ref 31 and were corrected for the real and imaginary parts of anomalous dispersion. All calculations and refinements were performed by using SHELX-76.[32]

Structural Analysis and Refinement. The systematically absent reflections confirmed the space group as $C222_1$ for the a,a and $P2_12_12_1$ for the e,e form. The positions of the bromine atoms were determined from a Patterson map and the remaining non-hydrogen atoms were located in subsequent Fourier syntheses. The structures were refined initially by a full-matrix least-squares procedure with independent isotropic temperature factors on the atoms. Absorption corrections were then applied. Hydrogen atoms were placed in their geometrically calculated positions [d(C–H) = 1.08 Å]. The final refinements were with anisotropic temperature factors on the non-hydrogen atoms and individual isotropic temperature factors on the H atoms. A two-block matrix least-squares method was employed. The function minimized was $w(|F_o| - |F_c|)^2$ where w is the weight. Final R = 0.032 for the a,a and 0.036 for the e,e form. No correction was applied for extinction. The final difference maps had no recognizable residual features. The figures were produced with CHEMGRAF.[33] The fractional positional parameters of the non-hydrogen atoms are presented in Table IV.

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Supplementary Material Available: Tables of hydrogen atom positional parameters (Table V), anisotropic thermal parameters (Table VI), interatomic distances (Table VII), and interbond (Table VIII), torsional (Table IX), and interplane (Table X) angles (11 pages); observed and calculated structure factors (29 pages). Ordering information is given on any current masthead page.

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Comparisons of Rate Constants for Thiolate–Disulfide Interchange in Water and in Polar Aprotic Solvents Using Dynamic ^{1}H NMR Line Shape Analysis

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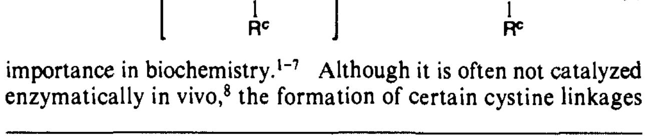
Abstract: The rate constants for representative thiolate–disulfide interchange reactions are larger in DMSO and DMF than in water by a factor of approximately 2300 at 24 °C. The log of the rate constant is directly proportional to the mole fraction of D_2O in mixtures of DMSO and D_2O, even at small mole fractions of D_2O. This linear proportionality suggests that thiolate anion is not specifically solvated by water and that hydrogen bonding is relatively unimportant in stabilizing this species. The values of $\Delta S^\ddagger$ for thiolate–disulfide interchange are approximately −10 cal/(deg mol), presumptively because of loss in the entropy of the reactants in going from ground to transition state, partially compensated by a gain in entropy from solvent release. Introduction of a hydroxyl group β to the C–S bond slows the reaction by a factor of 2–15; the introduction of methyl groups β to the C–S bond slows the rate by factors of 3–20. A number of substances have been screened as potential catalysts for thiolate–disulfide interchange in water: none showed useful levels of catalytic activity, although phenylselenol did accelerate the interchange significantly.

This paper examines the influence of solvent on rate constants for thiolate–disulfide interchange (eq 1: nuc = nucleophile, c = central, lg = leaving group). This reaction is one of broad



$$R^{nuc}S^- + \underset{\underset{R^c}{|}}{S}\text{—}SR^{lg} \rightleftharpoons \left[R^{nuc}\overset{\sim 1/2-}{S}\text{---}\underset{\underset{R^c}{|}}{S}\text{---}\overset{\sim 1/2-}{SR^{lg}}\right]^\ddagger \rightleftharpoons R^{nuc}S\text{—}\underset{\underset{R^c}{|}}{S} + {}^-SR^{lg} \quad (1)$$

importance in biochemistry.[1-7] Although it is often not catalyzed enzymatically in vivo,[8] the formation of certain cystine linkages in proteins may be enzyme catalyzed.[9-14] Many aspects of the mechanism of thiolate–disulfide interchange are understood:[15-22]

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