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Conformational Dependence of the Disulfide Stretching Frequency in Cyclic Model Compounds

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Abstract: Disulfide stretching frequencies and framework torsion angles are reported for 12 S–S bonds that occur in 7 crystalline, cyclic molecules, 2 of which are CH_2, CD_2 isotopomers. The S–S stretching frequency increases with increasing CCSS torsion angle above about 100° but is insensitive to this angle over the range 37–100°. Normal coordinate calculations using an optimized Urey–Bradley force field confirm that the observed behavior has a conformational origin. Collectively, the results support and somewhat extend the Sugeta, Go, and Miyazawa picture of the conformational dependence of the disulfide stretching frequency.

In biological systems the formation of disulfide bonds between cysteine residues can play an important part in establishing specific conformations of a protein molecule. In many instances the cysteines are separated by only a few (or no) amino acids, leading to disulfide loops having ring sizes in the range $8 \leqslant n \leqslant 20$. Examples of these include malformin A ($n = 8$),[1] thioredoxin ($n = 14$),[2] the neurotoxin *Siamensis* ($n = 17$ and 20),[3] and several analogues of oxytocin[4] and vasopressin ($n = 20$).[5]

Particular local conformations may influence the biological activity of such molecules, and hence there is considerable interest in methods that can elucidate their structures. Prompted by the observations of Lord and Yu[6] that the Raman spectra of lysozyme, ribonuclease, and α-chymotrypsin differed in the S–S stretching region near 500 cm^{-1}, there have been a number of attempts to establish how this frequency varies with the conformation proximate to the S–S bond in molecules containing CCSSCC fragments.[7]

The two most frequently cited correlation proposals, those of Sugeta, Go, and Miyazawa[8-10] and Van Wart and Scheraga,[11,12] present conflicting interpretations of Raman bands often observed near 525 and 540 cm^{-1} in the spectra of proteins and model primary disulfides. Sugeta et al. assign these bands to conformations having either one (525 cm^{-1}) or two (540 cm^{-1}) carbon atoms anti to a distal sulfur, i.e., one or two CCSS torsional angles ~180°.

Van Wart and Scheraga, however, assign them to structures having either one (525 cm^{-1}) or two (540 cm^{-1}) so-called A conformations. Their A conformation is one in which a CCSS torsion angle has a small value, roughly in the range 20–50°. In the case of unbranched disulfides, a hydrogen atom bonded to the second carbon atom then lies almost over, and perhaps interacts with,[13] the distal sulfur.

An examination of the Science Citation Index shows that the recent literature is rich with references to these leading articles. In those papers that include Raman data for specific proteins, this interpretational conflict has been handled in several ways. Some authors acknowledge it and provide an either/or discussion of the experimental spectra. Others clearly favor one or the other interpretation but often do not state explicitly that they are doing so. Occasionally, authors even side with one interpretation but reference only the other one.

To provide further evidence bearing on this important question we have prepared and studied six cyclic molecules, each of which has one or more disulfide bonds flanked by at least two methylene groups. Both crystallographic and spectroscopic measurements have been made, but in this paper we shall concentrate on the latter and invoke the necessary structural information without explication.

Experimental Section

Materials. Syntheses have been published previously for 1,2,6-trithiacyclononane (I),[14] 1,2,5,6-tetrathiacyclooctane (II),[15] 1,2,6,7-tetrathiacyclodecane (III),[16] and 1,2,6,10,11,15-hexathiacyclooctane (VI).[14]

Compound IV, 1,2,6-trithiacyclodecane, was prepared in a three-step synthesis. First, allyl alcohol and 1,4-butanethiol were reacted for 4 h at 100 °C to produce 5-thia-8-hydroxyoctanethiol, which was recovered by fractional distillation at 0.025 torr. This compound was converted to 4-thiaoctane-1,8-dithiol by refluxing it with thiourea and HCl, followed by NaOH, according to the procedure of Rosen and Busch.[17] The dithiol was then cyclized with iodine and triethylamine under high-dilution titrimetric conditions[14] in chloroform solution. After an extraction with dilute HCl, the chloroform was stripped and a portion of the resulting oil was column chromatographed on silica gel using CH_2Cl_2 as the eluant to yield IV as a white crystalline solid, mp 56.5–57.5 °C, after recrystallization from hexane.

Compound V, 1,2,5,6,9,10-hexathiacyclododecane, was obtained by performing a 100 °C (0.05 torr) sublimation on the same reaction mixture that gave II as the fraction subliming at 60 °C (0.05 torr).[15] Recrystallization of the crude sublimate from hexane gave white crystalline V, mp 73.5–74.5 °C.

The perdeuterio isotopomer of compound II was also synthesized. The bis(thiouronium) salt of 1,2-dibromoethane-d_4 was prepared and reacted with KOH to yield 1,1,2,2-tetradeuterio-1,2-ethanedithiol. The same procedure used to give II with the ordinary dithiol[15] was then followed to obtain II-d_8, mp 64.0–65.0 °C, from hexane.

Crystal structures have been published for compounds II[15] and III.[16] The remainder were determined by M. M. Olmstead (compounds I, IV, and V) and H. Hope (compound VI) of this department. The structures all show typical bond distances and bond angles for relatively unstrained cyclic molecules; i.e., SS distances 2.03–2.05 Å, CS distances, 1.82–1.84 Å, CC distances 1.52–1.54 Å, ring angles at C of 113–117°, and ring

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Table I. Disulfide Stretching Frequencies (cm^{-1}) in Crystalline and Dissolved Cyclic Disulfides

	RCCSSCCR′ torsion angles[b]/deg					Raman shift[c]	
disulfide species[a]	RC–C	C–S	S–S	S–C	C–CR′	cryst	soln[d]
I	–61	–56	121	–59	–62	507	506
IIa	–60	–48	117	–41	–63	504	507
IIb	–60	106	–86	105	–63	521	524
III	–74	–62	79	37	–160	502	505
IV	–48	–81	82	42	–156	506	502
Va	–54	–63	89	54	176	506	504
Vb	66	–90	–89	–175	–54	528	525
Vc	176	100	–104	78	66	(506)	(504)
VIa	63	52	79	176	–70	524	509,524
VIb	179	54	78	177	172	524	

[a] Molecule I, 1,2,6-trithiacyclononane; II, 1,2,5,6-tetrathiacyclooctane; III, 1,2,6,7-tetrathiacyclodecane (centrosymmetric); IV, 1,2,6-trithiacyclodecane; V, 1,2,5,6,9,10-hexathiacyclododecane; VI, 1,2,6,10,11,15-hexathiacyclooctadecane. [b] Defined according to the IUPAC-IUB Commission on Biochemical Nomenclature: *Biochemistry* **1970**, *9*, 3471. [c] Measured with a Spex Ramalab instrument at a 2-cm^{-1} slit width using 488-nm argon ion radiation. [d] In deuteriochloroform solution.

SSC angles in the range 103–108°.

Methods. Raman spectra of samples contained in glass capillaries at room temperature were obtained with a Spex Ramalab instrument using a 2-cm^{-1} slit width. The excitation source was the 488-nm argon ion line from a Spectra-Physics Model 164-02 mixed-gas laser equipped with an interference filter. Infrared spectra of KBr pellets of several of the powdered solids were obtained with a Perkin-Elmer Model 180 spectrometer.

Normal coordinate calculations were performed on Burroughs B7800 and VAX 11/780 computers using a suite of programs assembled in this laboratory. The vibrational problem is solved by the standard Wilson GF-matrix method, employing mass-weighted Cartesian coordinates. The B-matrix is calculated with a subroutine written by W. H. Fink, based on the work of Gwinn,[18] and the potential energy matrix is constructed by using Overend and Scherer's Z-matrix formalism.[19] As Gans[20] has advocated, force constants were determined by using the iterative second-order refinement procedure of Fletcher and Powell.[21]

Results

For all the solid compounds studied, whether as single crystals or as powders, the Raman spectra in the 500-cm^{-1} region showed only sharp, symmetrical lines whose appearance was independent of both the irradiation time and the incident laser power. In solution, however, ring opening and subsequent polymerization were sometimes noted. This phenomenon was invariably signaled by increased spectral noise and by the progressive growth of a feature near 525 cm^{-1}.

The major observations that bear on the question of the conformational dependence of the disulfide stretching frequency are assembled in Table I. Column 1 of this table both identifies the molecules studied and codes the conformationally distinct disulfide bonds for those molecules that have more than one of them. This phenomenon was invariably signaled by increased spectral noise and by the progessive growth of a feature near 525 cm^{-1}. Columns 3–5 contain the torsion angles pertinent to each CCSSCC fragment, while columns 2 and 6 specify its mode of attachment to the remainder of the molecule. Columns 7 and 8 show that except for molecule VI, only trivial changes in the disulfide stretching frequencies occur when these molecules are dissolved. Thus we infer that their dominant free-molecule conformations must be essentially the crystallographic ones. The solution spectrum of the 18-membered ring macrocycle VI shows both the 524-cm^{-1} line found for the crystal and another one at 509 cm^{-1} that is the more intense of the two by about 25%. Nevertheless, a substantial fraction of the disulfide bonds in dissolved VI evidently have local conformations similar to that found in the crystal.

Unambiguous frequency-conformation identifications are apparent for molecules I, III, IV, and crystalline VI. The assignments given in Table I for the two different disulfide bonds in molecule II were made initially on the basis of the structural similarities between configurations I and IIa. Similarly, the two disulfide bonds in crystalline VI and conformation Vb all have a methylene carbon atom anti to a distal sulfur, and Vb was assigned accordingly. Although molecule V has three SS bonds, its spectrum shows only two lines in the disulfide region, the one at 506 cm^{-1} being the more intense by almost a factor of 2. Conformation Va is similar enough to both III and IV to make its 506-cm^{-1} assignment fairly secure. Conformation Vc is unique, and initially it was assigned the lower frequency solely on intensity grounds.

Table II. Urey–Bradley Force Constants[a] for Cyclic and Acyclic Dialkyl Disulfides

constant	cyclic[b]	acyclic[c]	constant	cyclic[b]	acyclic[c]
	Stretching			Repulsive	
K(CH)	4.26	4.30	*F*(HCH)	0.044	0.20
K(CC)	2.45	2.53	*F*(CCH)	0.43	0.36
K(CS)	1.80	1.75	*F*(CSH)	0.43	0.39
K(SS)	2.28	2.27	*F*(CCC)	0.65	0.23
			F(CCS)	0.25	0.43
	Bending		F(CSS)	0.32	0.25
H(HCH)	0.44	0.35			
H(CCH)	0.30	0.31		Torsional	
H(SCH)	0.19	0.18	*Y*(CC)	0.15	0.09
H(CCC)	0.43	0.32	*Y*(CS)	0.061	0.045
H(CCS)	0.32	0.19	*Y*(SS)	0.076	0.15
H(CSS)	0.16	0.18			
				Internal Tension	
			κ(SCHC)	–0.004	
			κ(SCCH)	–0.023	

[a] Given in units of mdyn Å^{-1} for *K*, *H*, and *F*, mdyn Å for *Y* and κ. [b] This work. [c] Reference 10.

Normal coordinate calculations provide strong support for the various empirical assignments just described. From among the several commonly used alternatives we chose the Urey–Bradley force field because it is of minimal size, and it is known to be transferable in many instances.[22] In addition, Sugeta[10] had already parameterized such a force field for acyclic aliphatic disulfides, thus providing a convenient departure point for the present work.

In the first set of calculations the Fletcher–Powell[21] method was used to produce independent optimal fits to the spectra of crystalline II and its perdeuterio isotopomer. Coordinates were available for the heavy atoms from the crystal structure, but the hydrogen atoms were not particularly well located, so these were positioned using CH bond distances of 1.09 Å, HCH angles of 107°, and H–S nonbonded distances of 2.40 Å throughout.

Only slight differences were found between the two sets of independently optimized force constants, and hence these were simply averaged to yield the final values which are listed in Table II. Table III compares the observed and calculated spectra of the two isotopomers of compound II and describes the motions in terms of the potential energy distributions. The overall average discrepancy between observed and calculated frequencies is 1.8%, but the model reproduces the disulfide stretching frequencies and

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Table III. Vibrational Spectra (cm^{-1}) of Crystalline 1,2,5,6-Tetrathiacyclooctane Isotopomers

perprotio				perdeuterio			
obsd	calcd	sym[a]	motion (PED)[b]	obsd	calcd	sym[a]	motion (PED)[b]
2960	2976	A, B	CH_2 as	2220	2193	A, B	CD_2 as
2930	2954	A, B	CH_2 as	2166	2177	A, B	CD_2 as
2910	2931	A, B	CH_2 ss	2132	2135	A, B	CD_2 ss
2895	2920	A, B	CH_2 ss	2122	2121	A, B	CD_2 ss
1408	1430	A, B	CH_2 sc	1105	1110	A	CC (70), CD_2 w, sc
1385	1417	A, B	CH_2 sc		1108	B	CC (70), CD_2 w
1290	1297	A	CH_2 w	1059	1057	B	CD_2 sc
	1296	B	CH_2 w	1038	1056	A	CD_2 sc
1270	1256	A	CH_2 w	1019	1016	A, B	CD_2 mixed, CS (13)
	1255	B	CH_2 w	1011	1015	A, B	CD_2 mixed, CS (11)
1190	1208	A, B	CH_2 w, tw	948	905	A, B	CD_2 tw
1180	1199	A	CH_2 w, tw	930			
	1198	B	CH_2 w, tw	922	862	A, B	CD_2 tw
1016	1020	A	CC (88)	814	830	A	CD_2 w, CC (12)
1010	1019	B	CC (88)		829	B	CD_2 w, CC (12)
906	853	B	CH_2 r, CS (17)	736	733	B	CD_2 r, CS (22)
898	851	A	CH_2 r, CS (13)	730	731	A	CD_2 r, CS (17)
819	826	A	CH_2 r, CS (21)	694	715	A	CD_2 r, CS (24)
809	824	B	CH_2 r, CS (21)		709	B	CD_2 r, CS (26)
666	663	B	CS (59), CH_2 tw	605	594	A	CS (54), SS (10),[c] SS (7)[d]
	661	A	CS (59), CH_2 tw	583	588	B	CS (54), SCD (38)
618	635	A	CS (80)	578	575	A	CS (45), CD_2 tw
608	633	B	CS (77)		567	B	CS (53), CD_2 tw
521	520	A	SS (82),[c] SCC (6)	511	510	A	SS (68),[c] SS (13),[d] CS (10)
504	505	A	SS (88),[d] SS (10)[c]	494	494	A	SS (73),[d] SS (18),[c] CS (6)
428	425	B	SCC (52), CS (19), SSC (10)	389	385	B	SCC (46), SSC (15)
421	412	A	SCC (46), SS (10)[c]	353	370	A	SCC (38), SSC (10), SS (6)[c]
288	297	A	ring mode	268	269	B	ring mode
272	295	B	ring mode	240	258	A	ring mode
265	258	B	SSC (82)	231	226	B	SSC (71)
248	241	A	SSC (90)		218	A	SSC (83)
156	154	A	SSC (58), SCC (28), SS tor (17)	164	151	A	SSC (49), SCC (16), CS tor (16)
138	139	B	SSC (57), SCC (13), CS tor (11)	146	132	B	SSC (60), SCC (16), CS tor (12)
	103	A	SS tor (45),[c] CC tor (30)		95	A	SS tor (44),[c] CC tor (32)
	77	B	CS tor (57), CC tor (38)		71	B	CS tor (52), CC tor (38)

[a] Symmetries based on nominal C_2 geometry. [b] Symbols: as = antisymmetric stretch; ss = symmetric stretch; sc = scissors; w = wag; tw = twist; r = rock; tor = torsion. [c] Disulfide bond conformation IIb in Table I. [d] Disulfide bond conformation IIa in Table I.

their remarkably large deuterium isotope shifts essentially perfectly. It is also apparent from the potential energy distributions that the two conformationally distinct disulfide bonds vibrate quite independently in this molecule.

The force field given in Table II was then used to calculate the vibrational spectrum of molecule III, again using positioned hydrogen atoms. Two additional force constants [H(CCC) and F(CCC)] were required, and they were obtained by performing an optimization during which all the others were held invariant. The observed and calculated spectra are listed in Table IV. Apart from obvious deficiencies in the CH stretching region, the overall agreement is satisfying, particularly for the S–S stretching frequency.

The Table II force field was next used to predict the skeletal vibrations of molecule V. In this calculation the CH_2 groups were replaced by mass-14 pseudoatoms located at the crystallographic carbon sites. The observed and calculated spectra are in excellent agreement, as shown in Table V. In this molecule considerable mixing of the two lower (and very similar) frequency disulfide stretching modes is evident, but the highest frequency motion is clearly localized in the disulfide bond having the anti conformation.

To the best of our knowledge, there are no known crystalline cyclic molecules having structures with two carbon atoms anti to distal sulfurs, but an examination of molecular models showed that nearly such an arrangement is possible for 1,2-dithiacyclododecane in what is almost certainly a high-energy conformation. The atomic coordinates for this hypothetical structure were determined by providing a library program with bond distances (CC = 1.53 Å, CS = 1.83 Å, SS = 2.04 Å) and bond angles (CCC = 113°, CCS = 115°, SSC = 105°) together with torsion angles estimated from a large-scale model of the structure. With the mass-14 methylene approximation, and with a disulfide fragment having CCSS torsion angles of 180° and −160° and a CSSC torsion angle of +90°, the force field of Table II yields a calculated

Table IV. Vibrational Spectra (cm^{-1}) of Crystalline 1,2,6,7-Tetrathiacyclodecane

obsd		calcd		
IR	Raman	A_u	A_g	motion[a]
2963	2968	2963	2963	
2942	2941	2956	2956	
2925	2921	2948	2948	
2872	2895	2942	2942	
2854	2870	2925	2925	
2790	2791	2916	2916	
1446	1443	1455	1455	
1415	1418	1439	1440	
1402	1401	1415	1415	
1331	1341	1355	1355	
1291	1285	1277	1277	
1262	1254	1265	1264	
1235	1244	1240	1240	
1174	1176	1221	1221	
1130	1116	1206	1206	
1040	1038	1051	1050	
999	997	1011	1011	
940	944	911	912	
838	844	833	834	CS + CCC
744	749	733	734	CS + various CH_2
685	684	718	717	
621	624	633	637	
502	502	505	504	SS
421	436	436	437	CS + CCC
346		341	328	SSC + SCC
	298	290	301	SSC + CCC
	231	206	196	SSC
	156	143	157	torsions + SSC
		104	89	torsions
			78	torsions

[a] Calculated frequencies >900 cm^{-1} involve only CH_2 and CC motions.

Table V. Skeletal Vibrations (cm^{-1}) of Crystalline 1,2,5,6,9,10-Hexathiacyclododecane

obsd (Raman)	calcd	obsd (Raman)	calcd
850	844		326
	840		313
	832	293	
819		277	
705	705		267
671			259
	663	249	248
657		230	
	649	204	208
637		182	189
612	611	170	166
	570		163
	569	150	
528	530[a]		113
	510[b]		87
506	507[c]		69
	437		54
429			43
412	416		43
350	357		

[a] PED: 84% SS conformation Vb (Table I), 7% CCS bend. [b] PED: 65% SS conformation Vc, 29% SS conformation Va. [c] PED: 67% SS conformation Va, 30% SS conformation Vc.

disulfide stretching frequency of 541 cm^{-1} (PED: 93% SS, 5% CCS bend).

Discussion

The results given in Tables I and V immediately confirm the Sugeta, Go, and Miyazawa contention that a 525-cm^{-1} disulfide stretching frequency is produced in primary dialkyl disulfides when one of the CCSS torsion angles approaches 180°. It is apparent from Tables I and III that a frequency in this range can also arise in cyclic systems when ring-closure constraints create two CCSS torsion angles in the 100–110° range.

With regard to the Van Wart and Scheraga A-conformation proposal, the results for molecules III and IV in Table I show that in at least these instances the closure of a CCSS torsion angle to as small as 37° does not elevate the disulfide stretching frequency. Conformations IIa, III, and IV are all such that a hydrogen atom on the second carbon approaches to within 2.65 Å of a distal sulfur; a distance that is some 0.4 Å shorter than the sum of the van der Waals radii of H and S. In these molecules the total energy undoubtedly is affected by the H–S interaction, but it seemingly has a negligible effect on the curvature of the potential function along the direction of the SS displacement coordinate since the observed spectra of II, II-d_8, III, and V could all be reproduced successfully with a simple Urey–Bradley force field; i.e., one that includes only next-nearest-neighbor interactions.

According to both our and Sugeta's[10] calculations, the conformational dependence of the disulfide stretching frequency in primary dialkyl disulfides originates from a coupling between the SS stretching and SCC bending modes that comes into play over the approximate range 100–180° in the CCSS torsion angle. It should be emphasized that within a given class of molecules the Urey-Bradley model, as both we and Sugeta have implemented it, uses a predetermined set of fixed values for all the force constants. The extent to which internal coordinates couple in a given normal coordinate is therefore determined solely by the molecular geometry.

It is perfectly obvious, however, that certain of the force constants must depend on the chemical identity of R in an $-RCH_2SS-$ fragment. Thus, molecules with similar local conformations but different functionalities might well have somewhat different disulfide stretching frequencies. We make this point because the single piece of direct experimental evidence that caused Van Wart and Scheraga[11] to reject the Sugeta correlations involved dithiodiglycolic acid, $HOOCCH_2SSCH_2COOH$. In a crystalline sample of this compound the disulfide stretching frequency was found to be 508 cm^{-1}, while in an unpublished X-ray study performed in Parthasarathy's laboratory, Frank[23] found a molecular structure with C_2 symmetry having CCSS torsion angles of 167°.

In the spirit of the preceding paragraph we sought to determine by model calculations whether it might be possible to find reasonable new force constants that would yield a 508-cm^{-1} disulfide stretching frequency for a hypothetical $[R-C(14)-S]_2$ molecule having a backbone configured with the Frank structural parameters as reported by Van Wart and Scheraga.[11] The size of R was also varied in these calculations, and over the mass range 15–50 its effect was at most a decrease of 6 cm^{-1} in the calculated disulfide stretching frequency.

Beginning with either the cyclic or the acyclic set of force constants in Table II, disulfide stretching frequencies in the range 535–540 cm^{-1} were calculated. These could be lowered to near 510 cm^{-1} only by drastically reducing the values of the force constants H(RCS) and F(RCS). Concurrently, however, radical mixing of the SS and CS stretching modes occurred, yielding two lines at 510 cm^{-1} (PED: 56% SS, 35% CS) and 550 cm^{-1} (PED: 38% SS, 51% CS). The unsatisfactory nature of this result then prompted the comprehensive examination of dithiodiglycolic acid which we communicated very recently.[24]

Briefly stated, we discovered that this compound crystallizes in two modifications: one with no molecular symmetry elements that has two gauche CCSS torsion angles and one with the previously observed C_2 structure having two anti CCSS torsion angles. Unfortunately, the species whose spectrum was obtained by Van Wart and Scheraga was the former rather than the latter (whose disulfide stretching frequency is actually 536 cm^{-1}), and hence the premise on which they based their A-conformation correlation scheme is incorrect.

In summary, the present results show that the Sugeta, Go, and Miyazawa correlations that were developed for acyclic disulfides are also applicable to cyclic systems, with the additional feature that in these a 525-cm^{-1} line may have other than a gauche–anti structural origin. Contrary to the Van Wart and Scheraga proposal, which now is empirically baseless, the disulfide stretching frequency does not increase when CCSS torsion angles are closed below 50°, but the range of angles over which this point has been explored is not large. It is conceivable that in the range 0–40° a small frequency increase predicted by Sugeta's calculations[10] might be observed, but the molecules used to test for this must be crystalline and also have "normal" CSSC torsion angles.[12] Examples of these may be hard to find.

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