STUDIES IN MOLECULAR STRUCTURE SYMMETRY AND CONFORMATION

V. On the Conformation of the Disulphide Group from X-ray Analysis

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ABSTRACT

X-ray structural data of compounds containing the disulphide group X—S—S—Y in open chain molecules are examined with regard to their symmetry and conformation (as well as the chirality in the case of non-centrosymmetric crystals). When X and Y are identical and do not have any asymmetric centres in them, the space group in most cases has a centre of inversion or at least a mirror (glide), signifying the presence of both enantiomers. When X and Y have both asymmetric centres, the space group is necessarily non-centrosymmetric and enantiomorphous. Eight out of ten cases involving cystine and its derivatives indicate a preference for left chirality while pure cystine in two crystalline forms has right chirality.

1. INTRODUCTION

THE conformation of the disulphide group X—S—S—Y is of considerable interest from several points of view. Its conformation in open chain molecules is well known to be non-planar and disymmetric similar to that of hydrogen peroxide with the torsion angle θ around —S—S— being around $\pm 90°$. In general, when X and Y are simple substituents and contain no asymmetric centres such compounds are optically inactive since the two conformers are readily interconverted by rotation around the single bond S—S, the energy barrier for rotation being small (about 5 kcal/mole). Attempts to resolve the two have therefore not been successful so far. However, if the groups X and Y are asymmetric, the two conformers need not have equal energy and consequently one may be preferred over the other. In fact, a typical example is the amino acid L-cystine which shows high negative optical rotation in solution in the visible region, contrasted with moderate positive values shown by most of the other L-amino acids. The high negative rotation of L-cystine has been attributed by Fredga (1950) to the disymmetric disulphide group.

An earlier analysis by Hordvik (1966) was concerned with correlating the torsion angle θ with the bond length —S—S— and the variation of bond order with the above angle. In the present paper we examine a different aspect of the results of X-ray analysis in the solid state, namely, (*a*) to study the symmetry and space group of the crystal structures and its dependence if any on the nature of the substituents; (*b*) When the groups X and Y contain asymmetric centres, to study the chirality of the —S—S— group in the solid state and to compare it with the ORD results in solution. In the latter case the compounds necessarily take up non-centrosymmetric enantiomorphous space groups and hence the chirality can be established *via* the X-ray anomalous scattering method (Bijvoet, 1954). The compounds studied in the second category are mostly L-cystine and its derivatives. We exclude from this study compounds which have the —S—S— group in a ring system or in which —S—S— acts as a bridge.

2. ANALYSIS AND DISCUSSION OF DATA

2.1. Groups X and Y with no Asymmetric Centre

Table I lists the crystal structures and the space group of compounds with X and Y containing no asymmetric centres. The first thirteen compounds have $X = Y$ while the last two have $X \neq Y$. It is interesting to note that all but one of these thirteen crystallize in space groups which contain either a centre of inversion or at least a glide plane. This necessarily implies that both conformers exist in these structures. The only exception in the above group is diphenyldisulphide which takes up the enantiomorphous space group $P2_12_12_1$ so that only one of the two conformers exists in a given crystal. It would be of interest to establish the absolute structures* of the crystal, so also in the case of the non-centrosymmetric structures such as *p*-bromophenyl disulphide (Ccc2).

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* X-ray anomalous scattering effects can be used in general, for any non-centrosymmetric crystal. Thus the effects may be detectable not only in enantiomorphous space groups but also in non-enantiomorphous crystals possessing symmetry element such as a mirror or glide. As has been pointed out elsewhere (Srinivasan, 1971), the term "absolute configuration" in such cases is rather misleading since it connotes, in the conventional sense, one of the non-superposable mirror images, and the term absolute structure would seem preferable. What is established in such cases is the absolute structure in relation to some physical property associated with directional asymmetry.

TABLE I

No.	Compound	θ	formula	Space group
1.	Diphenyl disulphide [Lee and Bryant (1969)]	96·2°	$C_6H_5.S—S.C_6H_5$	$P2_12_12_1$
2.	*p, p'*-Dibromophenyl disulphide [Toussant 1945)]	..	$Br.C_6H_4.S—S.C_6H_4.Br$	Ccc2
3.	*p*-Dinitrophenyl disulphide [Ricci and Bernal (1969)]	..	$NO_2.C_6H_4.S—S.C_6H_4.NO_2$	C2/c
4.	Orthodinitrophenyl disulphide [Ricci and Bernal (1969)]	..	$NO_2.C_6H_4.S—S.C_6H_4.NO_2$	$P2_1/c$
5.	2-2'-Diaminodiphenyl disulphide [Gomes deMesquita (1967)]	± 87°	$NH_2.C_6H_4.S—S.C_6H_4.NH_2$	Pbca
6.	Dibenzyl disulphide [Lee and Bryant (1969)]	± 92.1°	$C_6H_5.CH_2.S—S\ CH_2.C_6H_5$	Cc or C2/c
7.	5-5'-Dithiobis (2-nitrobenzoic acid [Shefter and Kalman (1969)]	± 76.4°	$NO_2.(COOH).C_6H_4.S—S.C_6H_4\ (COOH).NO_2$	Pccn
8.	Dimethane-sulphonyl disulphide [Sorum 1953)]	..	$CH_3.S(O_2).S—S.S(O_2).CH_3$	$P2_1/c$
9.	Formamidinium disulphide monohydrate (as di-iodide) [Foss *et al.*, (1958)]	±104.8°	$(NH_2)_2C.S—S.C(NH_2)_2$	Pccn
10.	Formamidinium disulphide (as dibromide) monohydrate [Foss and Johnsen (1957)]	±89.2°	$(NH_2)_2C.S—S.C(NH_2)_2$	P2/c
11.	Formamidinium disulphide (as dichloride) [Foss *et al.*, (1958)]	..	$(NH_2)_2C.S—S.C(NH_2)_2$	Pbca
12.	Tetramethylthiuram disulphide [Maroy (1965)]	±88°	$(CH_3)_2N.C(=S).S—S.C(=S).N(CH_3)_2$	C2/c
13.	Tetraethylthiuram disulphide [Karle, Estlen and Britts (1967)]	±96.4°	$(C_2H_5)_2N.C(=S).S—S.C(=S).N(C_2H_5)_2$	$P2_1/c$
14.	*t*-Butyl N-N-dimethyl trithio percarbamate [Mitchell (1969)]	±99.6°	$(CH_3)_3C.S—S.C(=S).N(CH_3)_2$	$P2_1/c$
15.	2-(2-pyridyl methyldithio) benzoic acid [Karle *et al.*, 1969)]	99.1°	$COOH.C_6H_4.S—S.CH_2(C_6H_4N)$	$P2_12_12_1$

TABLE II

No.	Compound	θ	Space Group	Formula
1.	L-Cystine [Oughton and Harrison (1959)]	+73·8	$P6_1$	COOH.CH(NH_2).CH_2.S—S·CH_2·CH(NH_2).COOH
2.	L-Cystine dihydrobromide [Peterson, Steinrauf and Jensen (1960); Ananthakrishnan and Srinivasan (1964)]	−81·3	$P2_12_12_1$	COOH.CH(NH_2).CH_2.S—S.CH_2.CH(NH_2).COOH.2HBr
3.	L-Cystine dihydrochloride [Steinrauf, Peterson and Jensen (1958)]	−79·2	C2	COOH.CH(NH_2).CH_2.S—S.CH_2.CH(NH_2).COOH.2HCl
4.	N-N′-diglycyl-cystine.$2H_2O$ [Yakel and Hughes (1954)]	−79·1	A2	$NH_2.CH_2.\overset{\overset{O}{\|}}{C}.NH.\underset{\underset{COOH}{\|}}{CH}.CH_2\cdot S—S.CH_2.$ $\underset{\underset{OOCH}{\|}}{CH}.NH.\overset{\overset{O}{\|}}{C}.CH_2.NH_2.2H_2O$
5.	L-Cystine diamide diHCl [Chaney and Steinrauf (1968)]	−81·4	$P2_12_12_1$	NH_2.CO.CH(NH_2).CH_2.S—S.CH_2.CH(NH_2).CO.NH_2.2HCl
6.	Mono (2, 4-dinitrophenyl) L-cystine [Chaney and Steinrauf) (1969)]	..	$P2_1$	COOH.CH.(NH_2).CH_2·S—S.$C_6H_4(NO_2)_2$
7.	L-Cystine (tetragonal) [Chaney and Steinrauf (1974)]	+69·3°	$P4_1$	COOH.CH(NH_2).CH_2.S—S.CH_2.CH.(NH_2).COOH
8.	4-4′-di (thiouridine) [Shefter and Kalman (1968)]	−87·3	$P2_1$	($C_5O_4H_9$) ($C_4N_2O_1H_3$).S—S.($C_4N_2O_1H_3$) ($C_5O_4H_9$)
9.	di-5 1-(2′deoxy-α-D-ribo furanosyl) uracilyl disulphide [Shefter, Kotick and Bardos (1967)]	−49·1	$P2_12_12_1$	($H_{11}O_5N_2C_9$) S—S ($C_9N_2O_5H_{11}$)
10.	L-cystine dimethyl ester di-hydrochloride monohydrate [Vijayalakshmi and Srinivasan (1975)]	−84·4	$P2_1$	$CH_3.O\cdot\overset{\overset{O}{\|}}{C}.CH(NH_2).CH_2.S—S.CH_2.CH$ $(NH_2)\overset{\overset{O}{\|}}{C}.O.CH_3.2HCl.H_2O$

It is of interest to remark here that there was controversial discussion as to whether the space group of dibenzyl-disulphide is Cc or C2/c [Dijk and Visser (1971); Einsphar and Donohue (1971) and Lee (1971)]. The use of anomalous scattering has resolved this problem (Srinivasan and Vijayalakshmi, 1972).

The spontaneous resolution observed in the case of diphenyl disulphide does not appear to be unique. Similar occurrences have been noted for example in inorganic disuphides (Foss, 1954) and also in organic peroxy compounds (Jeffrey *et al.*, 1964). In fact, the simplest of such a disymmetric molecule is hydrogen peroxide (Srinivasan, 1970). It crystallises in the enantiomorphous space group $P4_12_12$ or $P4_32_12$ (Abraham, Collin and Lipscomb, 1951)[1].

While the enantiomorphous nature of the space group demands in all these cases, only one of the conformers to be present in a given crystal, the possibility of a single crystal containing microdomains of the enantiomorphous regions is not ruled out at least in a few cases where conditions are favourable. In fact, Sax and McMullan (1967) suggested the possible existence of such microdomains in the case of dibenzoyl peroxide considering the diffuse scattering intensity and the geometry of packing of the molecule in the unit cell. The above possibility may be verifiable by the use

of X-ray anomalous scattering technique, since the presence of equal amounts of such domains should give practically zero Bijvoet differences. This aspect is being pursued in this laboratory.

The last two compounds have $X \neq Y$ and one of them takes up the enantiomorphous space group $P2_12_12_1$ while the other is centrosymmetric ($P2_1/c$).

2.2. Groups X, Y with Asymmetric Centres

Table II lists compounds with X and Y containing asymmeric centres. In all the cases excepting (6), the two groups are the same ($X = Y$). As is to be expected they all take up non-centrosymmetric enantiomorphous space groups. Eight of the cases are L-cystine derivatives. Since the absolute configuration of the L-amino acid is known from X-ray anomalous dispersion method, this may be used as a reference to deduce the absolute conformation of the disulphide group in these crystals. In five of these cases, namely, (2) to (5) and (10), the chirality of the disulphide group is left (dihedral angles negative, around $-80°$) while in the two forms (1) and (7) of pure L-cystine alone it is right (positive, namely 71°). Structural details for (6) are lacking. The two compounds (8) and (9) which are not cystine derivatives also have left chirality.

Thus, while all the derivatives of L-cystine indicate a preference for left chirality, for pure cystine alone (both hexagonal and tetragonal forms) the indication is to the contrary. A firm conclusion is therefore not possible although, if we ignore differences between the pure form and the derivatives, there is an overall preference for left chirality.

These may be taken to be in broad agreement with the results of ORD and CD studies in solution for disulphide group in ring system (Carmack and Neubert, 1967; Claeson, 1968; *see* also Linderberg and Michl, 1970). However these have to be reckoned with caution since our data concern primarily with open chain molecules. Semi-empirical methods for energy calculations may be expected to throw light on this aspect. These are being investigated and the results will be reported in due course.

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