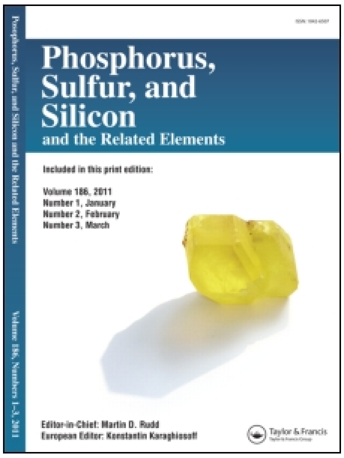

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STEREOCHEMISTRY OF INCIPIENT ELECTROPHILIC AND NUCLEOPHILIC REACTIONS AT DIVALENT SELENIUM CENTER: ELECTROPHILIC-NUCLEOPHILIC PAIRING AND ANISOTROPIC SHAPE OF Se IN Se···Se INTERACTIONS

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Using the Cambridge Crystallographic Data Base and computer retrieval methods, we have studied the preferred directions of approach of nucleophiles and electrophiles at divalent selenium centers. We find that electrophiles approach Se in a direction nearly normal to the selenide plane Y–Se–Z while nucleophiles approach Se nearly in the selenide plane and along the back side of Y–Se or Z–Se bonds. We also found evidence for the incipient formation of attractive electrophile-nucleophile pairing in Se···Se interactions. Other Se···Se contacts which did not fit the above pattern showed non-spherical effective shape for Se atoms. The preferred directions of approach of electrophiles and nucleophiles for Se and S are very similar and may be understood in terms of frontier orbitals. Such similarity in the shape and orbital environment of S and Se indicate to some extent how Se can play the role of S in some enzymes.

INTRODUCTION

Selenium is an important component of several biological macromolecules such as formate dehydrogenase, glycine reductase, nicotinic acid hydroxylase and glutathione peroxidase. Nevertheless, appreciation of the toxicity of selenium and selenium containing compounds is more widespread than the appreciation of the essential nature of selenium in many functional proteins.[1] However, it is becoming increasingly evident that there are many enzymes that are selenium dependent and also that selenium is able to substitute for sulfur in many biological molecules. For instance, when organisms receive more than micromolar concentrations of selenium, some enzymes begin to substitute selenium for sulfur in many cellular constituents.[1] Se has valencies ±2, 4, 6 like S and is a third row element in the periodic chart. Since selenium can be substituted for sulfur, it is logical to assume that some of the important electronic and chemical interactions of these two elements with other atoms are very similar. Also, the van der Waals radius[2] for these two atoms differ only slightly ($S = 1.85$; $Se = 2.0$ Å) suggesting that sterical interactions of sulfur with other moieties in a macromolecule could be closely mimicked by selenium. The similarities in structural roles between selenium containing proteins and sulfur containing

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proteins may be inferred from the following observation. Selenium can only occur as selenomethionine and selenocystine in proteins; the crystal structure of DL-selenomethionine is isomorphous with α-DL-methionine.[3] Also, the geometries and conformations of diselenide and disulfide groups are very similar.[4]

Recently our analysis of the interactions of sulfur with electrophiles and nucleophiles[5] in crystals has given insight into the preferred direction of approach of electrophiles and nucleophiles toward sulfur. It was also found that the pattern of S···S interactions in crystals for a majority of these interactions may also be regarded as the incipient formation of an attractive electrophile-nucleophile pairing. If selenium also exhibits similar chemical and electronic characteristics, then the substitution of selenium for sulfur in many macromolecules could be understood in terms of the similarities in the characteristics of sulfur and selenium. We have, therefore, analyzed the non-bonded atomic contacts with selenium and found that (i) electrophiles approach selenium nearly along the p_z orbital normal to the selenide plane (ii) nucleophiles approach selenium in the selenide plane along the σ^* orbital on the back side of one of the selenide bonds, and (ii) Se···Se contacts show a reciprocal electrophilic-nucleophilic pairing.

METHOD

The crystallographic data used in this analysis were retrieved from the Cambridge structural data base.[6] The 1984 update contains over 40,000 structures of which 128 have a C–Se–C or a C–Se–Se fragment.† The criteria used to select data containing such a fragment are as follows: (1) Each structure contains at least one C–Se–C or C–Se–Se fragment and the coordinates for these have been deposited; (2) only interatomic distances, $d_{Se\cdots X}$ between Se and X (= O, N, S, Se, Cl, Br, I, F and metal ions) less than the sum of their van der Waals radii (i.e. $d < r^w_{Se} + r^w_X$) were taken to be short contacts and were stored for further analysis; (3) since intramolecular contacts may be constrained to be so due to covalent forces, we considered only intermolecular contacts and (4) we considered only the shortest of all contacts with selenium (i.e. Δr is greatest, where $\Delta r = r^w_X + r^w_{Se} - d_{Se\cdots X}$) using the radii given by Bondi.[2] For all contacts that survived the closest contact criterion the parameters[5] θ and ϕ (see Figure 1) were calculated and used for further analysis. The data are presented in Tables I and II and Figures 2, 3, 5 and 6 as scattergrams.

RESULTS AND DISCUSSION

Directional Preference of Electrophiles and Nucleophiles[7,8]

The interatomic contacts (Table I) were analyzed using the spherical polar coordinates, θ and ϕ, specifying the directions of Se···X with reference to the selenide plane Y–Se–Z (Figure 1) where the approaching atom X is either an

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† The bibliography of these entries are available from the authors and the Editor-in-Chief.

TABLE I

Interatomic Se···X contacts

Ref code	Se	X	Se···X	Theta	Phi
Electrophiles					
BIHSAM	SE1	PT1	2.376	25.7	180.0
BIHSAM	SE2	PT1	2.400	22.1	69.9
BIMTIA	SE1	PT1	2.564	26.0	174.1
BIMTIA	SE2	PT2	2.563	24.4	178.1
BIZZAL	SE1	RE1	2.572	23.3	172.6
BIZZAL	SE2	RE1	2.585	24.0	168.6
BOSEPT	SE1	PT1	2.430	27.5	176.7
BRSERE	SE1	RE1	2.604	28.4	167.9
BSEMEP	SE1	PT1	2.598	20.8	177.0
BSEMEP	SE2	PT2	2.590	24.0	171.3
DPSEHG	SE1	HG1	2.702	19.9	176.0
DPSEHG	SE2	HG1	2.801	14.5	167.0
DPSEHG01	SE1	HG1	2.653	21.2	173.7
DPSEHG01	SE2	HG1	2.918	13.5	169.5
ESEPDC	SE1	PD1	2.423	20.9	170.2
PDSECL	SE1	PD1	2.403	22.7	176.2
PDSECL	SE2	PD1	2.364	25.4	174.7
Nucleophiles					
BEBVOT	SE3	F1F	3.196	75.1	141.2
BOSECH	SE1	O4A	3.456	57.6	153.2
BOWSUB	SE1	N2B	3.287	73.5	133.1
BUCKUF	SE1	BR1C	3.378	89.9	110.7
BUCKUF	SE4	BR2E	3.334	89.3	111.8
CLPHSE	SE1	CL1B	3.663	76.3	135.7
CLPHSE	SE2	CL2D	3.775	81.6	134.3
DTSEYL	SE1	O1B	3.461	87.9	165.8
FSEANT	SE1	F5A	3.185	85.9	133.9
FSEANT	SE2	F3G	3.271	89.7	142.7
MESEFV	SE12	F1E	3.233	76.8	142.0
MSEHPD	SE1	O1A	3.476	77.9	108.8
PFPDSE01	SE11	F6A	3.328	84.7	166.4
PTSTCQ	SE1	N2D	3.106	86.6	122.6
SECNBZ	SE1	N1C	3.058	85.1	133.1
SEFORC10	SE1	CL1A	3.187	89.4	128.4
SEINDI	SE1	O1E	2.982	67.5	141.0
SEURBR	SE3	BR2F	3.720	89.6	136.4
TSEBZT	SE1	S4A	3.724	44.3	124.7
TSETCL10	SE2	CL1B	2.936	76.4	134.1
Nucleophiles but showing electrophilic character					
DSEIOD	SE1	I2	2.829	17.5	178.1
OXSEIC	SE1	I1	2.630	17.3	167.7
OXSELI	SE1	I2	2.755	20.7	167.6
PHSECL	SE1	CL1	2.291	5.1	2.2
THSELI01	SE3	I2	2.766	20.0	157.7

electrophile (e.g. metal ions) or a presumed nucleophile (e.g. X = F, I, Br, Cl, N or O). The 42 contacts fall mainly into two types (Figures 2 and 3). Nearly all type I contacts (17) are with electrophiles with $\langle \theta \rangle = 23(4)^\circ$ and type II contacts (20) are with nucleophiles with $\langle \theta \rangle = 79(11)^\circ$. Figure 3 indicates clearly that type II contacts tend to approach along the back of one of the covalent bonds to Se with $\langle \theta \rangle = \pm 135(15)^\circ$. Interestingly, a few halogen atoms of R–X groups engage in type I contacts as well. In all these cases (denoted by ⊙ in Figures 2 & 3), a Se

TABLE II

Interatomic Se···Se contacts

Ref code	Atom I	Atom J	Dist I–J	Theta	Phi
BALWEQ	SE1	SE11C	3.865	73.4	169.9
BALWEQ	SE11	SE1C	3.865	73.9	139.8
BIDFAV	SE1	SE1A	3.611	80.6	132.0
BIDFAV	SE1A	SE1	3.611	80.6	132.0
BIOTNC	SE1	SE1A	4.032	15.9	5.2
BIOTNC	SE1A	SE1	4.032	69.9	138.5
BIOTNC	SE1	SE1B	4.032	69.9	138.5
BIOTNC	SE1B	SE1	4.032	15.9	5.2
BIXBIT	SE4	SE4F	3.727	72.1	143.1
BIXBIT	SE4F	SE4	3.727	72.1	143.1
BIYNAY	SE1	SE2D	3.467	60.4	159.7
BIYNAY	SE2	SE1C	3.467	80.8	119.7
BOHBOP	SE2	SE2D	3.816	72.0	147.3
BOHBOP	SE2D	SE2	3.816	72.0	147.3
BOJCOS	SE1	SE1A	2.930	16.3	164.6
BOJCOS	SE1A	SE1A	2.930	89.3	157.0
BOZFUR	SE1	SE12A	3.893	21.7	73.2
BOZFUR	SE12	SE1A	3.893	22.0	107.2
BUHCOW	SE2	SE2D	3.676	70.9	148.3
BUHCOW	SE2D	SE2	3.676	70.9	148.3
CSEBZT	SE1	SE1A	3.745	80.9	125.8
CSEBZT	SE1	SE1B	3.745	19.9	24.4
CSEBZT	SE1A	SE1	3.745	19.9	24.4
CSEBZT	SE1B	SE1	3.745	80.9	125.8
DPHDSE	SE1	SE11A	3.844	75.3	179.9
DPHDSE	SE11	SE1B	3.844	43.7	146.3
DSELAC	SE1	SE1C	3.803	89.2	152.6
DSELAC	SE1C	SE1	3.803	89.2	152.6
FSEANT	SE1	SE2A	3.853	80.1	176.3
FSEANT	SE2	SE1F	3.853	6.3	136.9
MORTRS1	SE1	SE1A	3.404	76.0	142.3
MORTRS1	SE1A	SE1	3.404	76.0	142.3
MOSEAN	SE1	SE2A	3.871	49.1	143.9
MOSEAN	SE2	SE1E	3.871	63.2	150.4
OXDSEN	SE1	SE2B	3.794	33.3	106.0
OXDSEN	SE2	SE1D	3.794	81.4	129.6
PSCHDA	SE13	SE13A	3.901	87.9	141.9
PSCHDA	SE13	SE13B	3.901	4.7	76.0
PSCHDA	SE13A	SE13	3.901	4.7	76.0
PSCHDA	SE13B	SE13	3.901	8.9	141.9
SECLUR	SE1	SE3D	3.808	84.8	128.0
SECLUR	SE3	SE1G	3.808	84.8	144.7
SELCBX	SE1	SE1C	3.965	54.6	179.3
SELCBX	SE1	SE1D	3.965	74.5	115.2
SELCBX	SE1C	SE1	3.965	74.5	115.2
SELCBX	SE1D	SE1	3.965	54.6	179.3
SESEPH	SE1	SE6A	3.900	19.7	18.1
SESEPH	SE6	SE1B	3.900	80.7	134.9
THPHSE	SE2	SE2C	3.619	74.9	111.5
THPHSE	SE2	SE2D	3.619	37.7	98.8
THPHSE	SE2C	SE2	3.619	37.7	98.8
THPHSE	SE2D	SE2	3.619	74.9	111.5
TMBDSE	SE1	SE2B	3.423	85.0	104.0
TMBDSE	SE2	SE1B	3.423	85.1	103.8
TSELOC	SE2	SE4F	3.668	18.5	6.3
TSELOC	SE4	SE2K	3.668	83.3	130.4

TABLE II (Cont'd)

Ref code	Atom I	Atom J	Dist I-J	Theta	Phi
TSEMOR1	SE1	SE1A	3.658	87.2	128.3
TSEMOR1	SE1	SE1B	3.658	23.3	179.9
TSEMOR1	SE1A	SE1	3.658	23.3	179.9
TSEMOR1	SE1B	SE1	3.658	87.2	128.3
TSEPIP1	SE1	SE2D	3.802	6.1	142.4
TSEPIP1	SE2	SE1D	3.802	85.4	141.4
TSETCN	SE1	SE1A	3.804	18.9	72.8
TSETCN	SE1	SE1B	3.804	18.9	107.2
TSETCN	SE1A	SE1	3.804	18.9	107.2
TSETCN	SE1B	SE1	3.804	18.9	72.8
XSTNON	SE3	SE3A	3.629	79.5	127.1
XSTNON	SE3A	SE3	3.629	79.5	127.1

atom approaches the halogen atoms in a "head-on" fashion, on the back side of the R–X bond. These halogen atoms are also involved in longer type II contacts, but in these situations, a Se atom approaches in a direction nearly normal to the R–X bond and the halogen atoms approach the Se atom along the back side of Y–Se or Z–Se bonds.[9] In all these contacts, the halogen atom forms a strong "coordination bond" with the Se atom, just like the metal ions. In fact, the interhalogen bond distance increases considerably and seems to be a function of Se–X bond distance; the shorter the Se–X bond distance, the longer the interhalogen bond length. These complexes could better be represented by a structure like $SeX^{\delta+}.X^{\delta-}$ than $Se.X_2$. Such a representation seems to be more meaningful since the coordinating halogen atom behaves more like an electrophile with θ values about 20° and the other halogen atom acts more like a nucleophile with θ values about 80° and ϕ values about 135°. These preferred

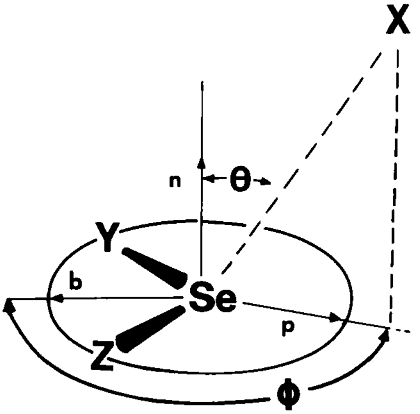

FIGURE 1 The polar angle $\theta(0<\theta<180°)$ and azimuthal angle $\phi(-180<\phi<180°)$ are spherical coordinates specifying the direction of Se···X. Vector **n** is normal to the selenide plane, b bisects angle Y–Se–Z and p shows the direction of Se···X projected onto selenide plane.

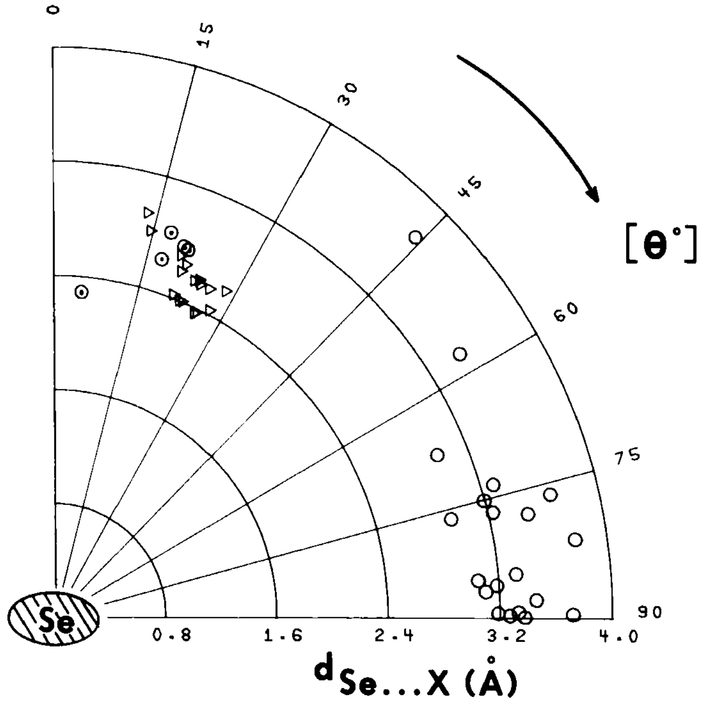

FIGURE 2 Scattergram of $d_{Se \cdots X}$ vs. [θ] indicating spatial distribution of Se···X contacts. [θ] is the lesser of θ or $180 - \theta$. Open circles represent contacts with nucleophiles and triangles with electrophiles. Striped area represents the selenide plane. ⊙ represents the head-on contacts with iodine atoms.

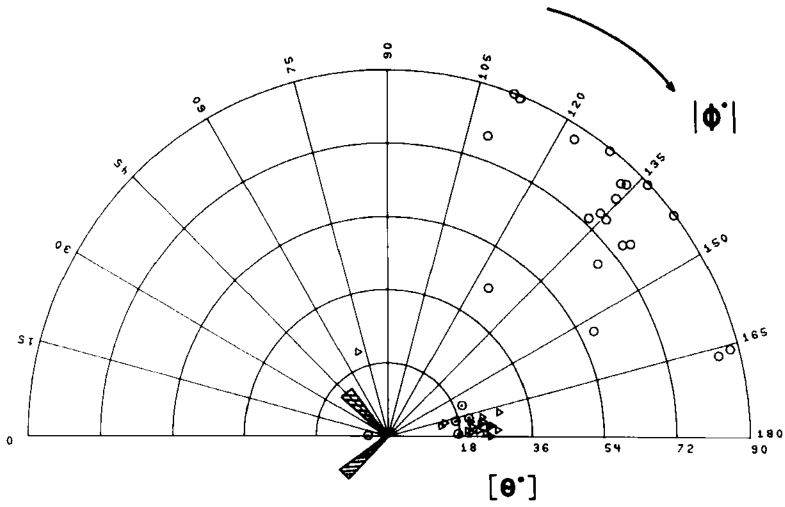

FIGURE 3 Distribution of Se···X contacts in the θ, ϕ space. $|\phi|$ is the absolute value of ϕ. No distinction is made between the contacts above and below the selenide plane or between Y–Se and Z–Se. Striped area represents Y–Se or Z–Se bonds.

directions of approaches of electrophiles and and nucleophiles to selenium may be explained in terms of the frontier orbitals[10] as for sulfur.[5] In type I contacts, electrophiles interact with a HOMO (which is essentially a Se lone pair p_z orbital) and approach Se, not along p_z but tilted with respect to p_z by about 20°. Also, the concentration of $|\phi|$ in the range 160–180° for electrophiles approaching Se (and S) indicates a preferred volume in space which the electrophiles seek for coordination. The approaches of the nucleophiles in the plane of the selenide along the back side of Y–Se or Z–Se bond identifies the LUMO as the anti-bonding σ^* orbital located on the back side of Y–Se or Z–Se.

Attractive Electrophilic-Nucleophilic Pairing.[11]

Of the 128 crystal structures containing divalent Se, 25 structures have 34 pairs of Se···Se contacts (Table II). A selenium atom Se_i not covalently linked to Se_j was considered to make a contact if the $\mathrm{Se}_i\cdots\mathrm{Se}_j$ distance was not greater than 4.0Å. Each $\mathrm{Se}_i\cdots\mathrm{Se}_j$ contact is associated with two sets of spherical polar cordinates (θ_i, ϕ_i and θ_j, ϕ_j) (see Figure 4). These values were calculated by a locally modified version of GEOM 78. The θ_i's and θ_j's are plotted against $d_{\mathrm{Se}\cdots\mathrm{Se}}$ in Figure 5. As for S, a majority of θ_i and θ_j values fall into classes corresponding to type I for θ_i's (electrophile) and type II for θ_j's nucleophile. The correlation of θ_i vs. θ_j for each pair of these contacts (Figure 6) illustrates that if one Se_i is regarded as an electrophile in terms of its θ_i, ϕ_i, the values θ_j and ϕ_j for the approach of the other selenium (Se_j) correspond to a nucleophile. The figure also reveals a preference for values of θ_i and θ_j(θ_i 30°; θ_j 80°) for type I and II contacts.

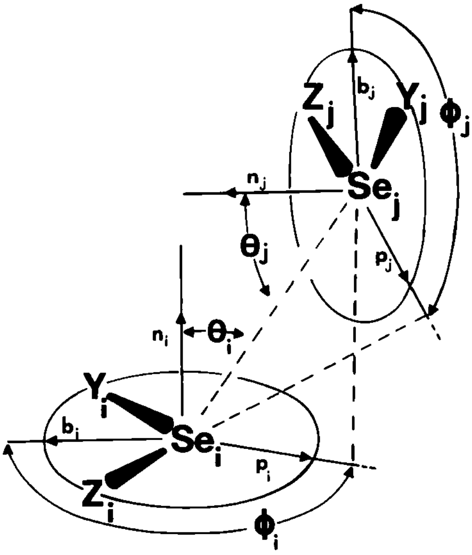

FIGURE 4 The approach of Se_j relative to the plane Y_i–Se_i–Z_i and Se_i relative to that of Y_j–Se_j–Z_j. All other parameters as defined in Figure 1.

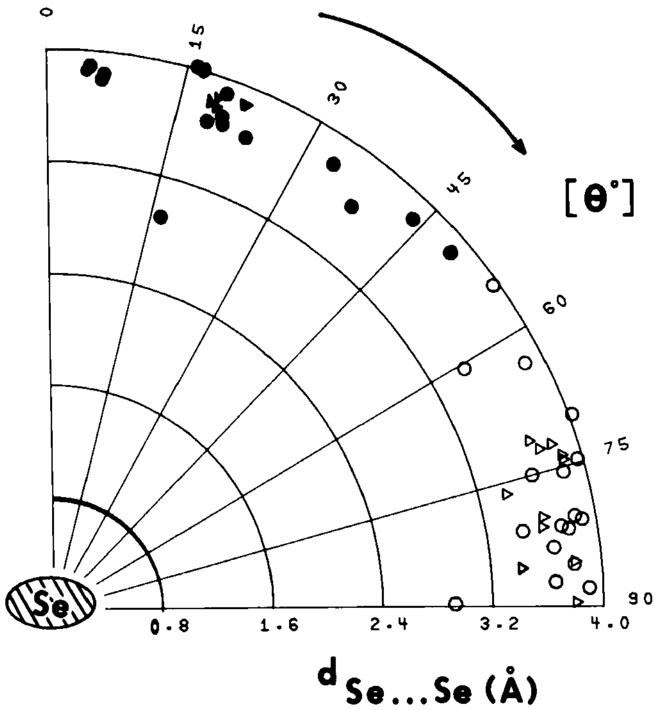

FIGURE 5 Polar graph of $d_{\mathrm{Se}\cdots\mathrm{Se}}$ vs. $[\theta]$. Of the two values of θ for each contact the lower one is represented by filled circles or triangles and the higher ones by open circles and triangles. Triangles define type III contacts. Overlapping symbols have been displaced for clarity.

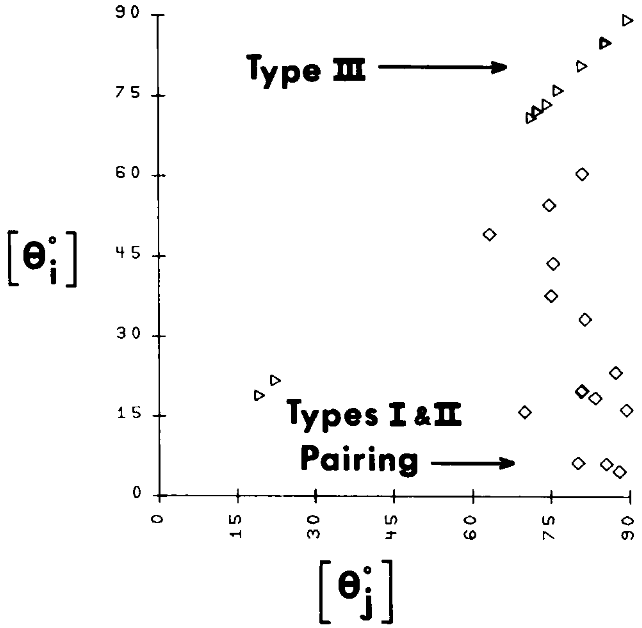

FIGURE 6 Shows correlation of $[\theta_i]$ vs, $[\theta_j]$ for each pair of contacts. The squares represent the type I and II pairing contacts.

Some contacts (13 pairs) denoted by triangles form a third group (type III) by themselves; for most of these contacts, $\theta_i = \theta_j$ due to a crystallographic symmetry (center of inversion or translation along **a**, **b**, or **c**). Type III contacts with the available data, show that near $\theta = 20°$ and $\theta = 80°$, the effective magnitude of Se···Se contact distances are different and hence, Se has non-spherical shape.[13] The average values of $d_{\mathrm{Se\cdots Se}}$ in the range of from 15 to 30° and from 75 to 90° are, respectively, 3.83(4) and 3.70(4) Å. Although, Se···Se interactions closely resemble S···S interactions in crystals, the complementary electrophile-nucleophile pairing for Se···Se interaction is much more pronounced than for S···S. It is quite remarkable that such similarities due to orbital interactions are evident in the environment around S and Se and they indicate to some extent, how in some enzymes, Se can play the role of sulfur.

ACKNOWLEDGEMENTS

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