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A Database Study of Nonbonded Intramolecular Sulfur–Nucleophile Contacts

BY F. TEMPLE BURLING* AND BARRY M. GOLDSTEIN†

Department of Biophysics, University of Rochester Medical Center, Rochester, New York 14642, USA

Abstract

A search of the Cambridge Structural Database (1991, version 4.5) was performed to investigate nonbonded intramolecular 1,4 S···O close contacts of the kind seen in the thiazole nucleoside tiazofurin and other classes of compounds. The search yielded 362 structures with 1,4 S···O connectivity. S···O distances in 70% of these structures were less than the sum of the sulfur and oxygen van der Waals radii. Findings indicate that 1,4 S···O close contacts are common and so probably result from intramolecular interactions rather than from external crystal packing forces. A structure containing a sulfur atom in a conjugated ring system is more likely to exhibit 1,4 S···O close contacts than a structure containing a sulfur atom in an unconjugated and/or acyclic environment. Sulfur–nitrogen contacts were also investigated and were found to show similar properties. These results are consistent with findings from previous quantum-chemical-based studies performed

on model fragments [Burling & Goldstein (1992). *J. Am. Chem. Soc.* 114, 2313–2320].

Introduction

The crystallographic literature contains numerous examples of both intermolecular and intramolecular nonbonded sulfur–nucleophile close contacts, in which the sulfur–nucleophile distance is less than the sum of the sulfur and nucleophile van der Waals radii (Rosenfield, Parthasarathy & Dunitz, 1977; Kucsman & Kapovits, 1985, and references therein). A previous survey of the Cambridge Structural Database (Kucsman & Kapovits, 1985, and references therein) found 755 structures, with various intramolecular sulfur–oxygen connectivities, displaying nonbonded sulfur–oxygen contact distances between 2.00 and 3.25 Å. The observation of this conformational feature in a large number of compounds indicates that an intramolecular interaction is responsible for these close contacts.

We have been interested in the biological significance of an intramolecular 1,4 sulfur–oxygen close contact seen in the crystal structure of the thiazole

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* Current address: The Howard Hughes Medical Institute, Department of Molecular Biophysics and Biochemistry, Yale University, New Haven, Connecticut 06511, USA.

† Author to whom correspondence should be addressed.

nucleoside antitumor agent tiazofurin (Fig. 1a) (Goldstein, Takusagawa, Berman, Srivastava & Robins, 1983). Similar close contacts are seen in eight inactive thiazole nucleoside analogs (Goldstein et al., 1983; Goldstein, Mao & Marquez, 1988; Burling, Gabrielsen & Goldstein, 1991; Burling, Hallows, Phelan, Gabrielsen & Goldstein, 1992).

The sulfur–O1′ distances in the crystal structures of these compounds lie in the range 2.773 (2)– 3.158 (4) Å. In all cases, this distance is less than the sum of the sulfur and oxygen van der Waals radii (3.3 Å) (Bondi, 1964). The presence of the S···O close contact in these structures, each of which crystallizes in a different packing environment, indicates that this interesting conformational feature results from a nonbonded intramolecular interaction. This interaction is the result of structural features shared by the thiazole nucleosides.

In an effort to explain the observed S···O close contacts in the thiazole nucleosides, ab initio and semiempirical quantum-chemical calculations were performed on the isolated thiazole ring and on larger thiazole nucleoside model fragments (Burling & Goldstein, 1992). In model fragments of the type shown in Fig. 1(b), computations indicate that close 1,4 S···O contacts result from an attractive electrostatic interaction between the positively charged thiazole sulfur and the nucleophilic oxygen corresponding to O1′ of the ribose ring. These computations further indicate that the positive charge on the sulfur atom is produced by the electron-with-

drawing environment of the conjugated ring. Donation of electrons to the π system of the ring leaves a significant net positive partial charge on the thiazole sulfur.

Calculations were also performed on the model fragment shown in Fig. 1(c), in which the divalent sulfur atom is in a fully saturated environment. In this fragment, the positive charge on the sulfur atom is substantially reduced, resulting in a decrease in the magnitude of the attractive interaction between the sulfur and oxygen atoms. As a result, a close S···O contact is not observed in the computed minimum-energy structure of the model fragment containing sulfur in a fully saturated acyclic environment (Burling & Goldstein, 1992).

These computational results suggest that the conjugated environment of the thiazole ring gives rise to the observed S···O1′ close contact in the thiazole nucleosides. Based on these results, one would predict that molecules containing divalent sulfur in a conjugated environment would be more likely to show intramolecular S···O close contacts than molecules that do not permit delocalization of the sulfur charge.

In order to test this hypothesis, a study of all molecules exhibiting 1,4 S···O connectivity was performed using the Cambridge Structural Database. S···O distances and related torsion angles were analyzed as a function of the bonding environment of the sulfur. Analysis of the molecules found in this search indicates that compounds containing a divalent sulfur atom in a ring system form closer 1,4 contacts with oxygen than do compounds with acyclic sulfur atoms. Further, compounds with sulfur atoms in conjugated ring systems form closer 1,4 S···O contacts than do compounds with sulfur atoms in saturated environments.

Computational results indicate that S···O close contacts result from a general electrostatic interaction. This suggests that close contacts should also be observed in other 1,4 sulfur–nucleophile-connected structures. Thus, the database was searched for structures exhibiting 1,4 close contacts between divalent sulfur and divalent nitrogen. This search showed that compounds with 1,4 S···N connectivity also form S···N close contacts, similar to those observed in structures having 1,4 S···O connectivity.
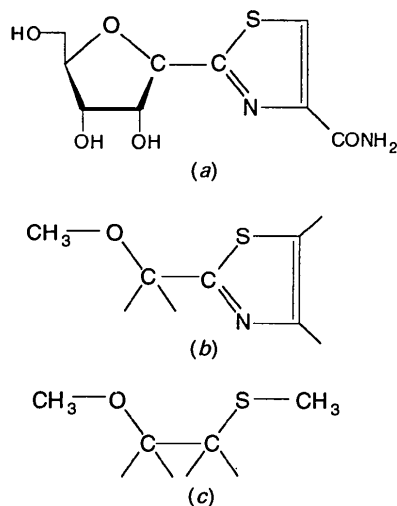

Fig. 1. (a) The antitumor agent tiazofurin, one example from the large class of compounds showing close 1,4 sulfur–oxygen contacts. (b) Model fragment with 1,4 sulfur–oxygen connectivity containing sulfur in a conjugated thiazole ring. Computed minimum energy structures of this fragment maintain the S···O close contact. (c) Model fragment with 1,4 sulfur–oxygen connectivity containing the sulfur atom in an acyclic fully saturated environment. Computed minimum energy structures of this fragment do not maintain the S···O close contact.

Methods

Searches of the crystallographic database were performed using the Cambridge Structural Database (CSD) (1991; see also Allen, Kennard & Taylor, 1983). Search fragments were constructed using the QUEST routine of the CSD system. Molecules found in these searches were subjected to structural and statistical analysis using the GSTAT routine.

Symmetry-equivalent fragments were removed after using the *GSTAT* routine, as the NOD (no duplicate) keyword of the *GSTAT* routine was found to be too discriminating in some cases and not selective enough in others. In order to test the hypotheses raised by the computational work on the thiazole nucleosides, initial searches were restricted to compounds containing divalent sulfur in 1,4 S⋯O-connected fragments. Subsequent searches were performed for structures containing 1,4 S⋯N-connected fragments. It should be noted that S⋯O close contacts are also seen in structures having 1,5 and 1,6 S⋯O connectivity, as well as structures having different valence states (S^{IV} and S^{VI}) of the sulfur atom (Kucsman & Kapovits, 1985, and references therein).

A preliminary search was performed to find all structures in the database containing 1,4 S⋯O connectivity using the search fragment with type-I geometry shown in Fig. 2. In compounds containing fragments with type-I geometry, the O4—C3—C2—S torsion angle (χ), and thus the S⋯O distance, is rigidly constrained when the C2—C3 bond is cyclic. We were interested only in those compounds for which rotation about this bond is unhindered. Thus, the C2—C3 bond was required to be acyclic in all of the search fragments used. Screens were also employed to retain only those compounds for which coordinates were available and which had R values of less than 10%. A sub-database was created containing the 362 compounds that satisfied these search criteria. This sub-database was used for all later connectivity searching (using *QUEST*) and statistical analysis of crystallographic data (using *GSTAT*) from structures containing fragments with 1,4 S⋯O

connectivity. Similar methods were used to produce a sub-database of 1,4 S⋯N-connected structures.

Additional fragments used in subsequent more restrictive searches of the sub-database of structures with 1,4 S⋯O connectivity are shown in the appropriate figures. With the exception of the sulfur atom, which was required to be divalent, only the minimum number of connected atoms in these search fragments are shown. Additional connections were allowed for the other atoms. Unless otherwise noted, all bonds were set to bond type 99 (any type of bond). Searches requiring an explicitly cyclic or acyclic environment were carried out using the appropriate bond descriptors in either the *QUEST* or *GSTAT* searches. For those searches requiring a conjugated environment, the appropriate bond descriptors were set to a variable bond type (VBT) that included both double and aromatic bonds (bond types 2 and 5). For searches requiring saturated environments, appropriate bond descriptors were set to the single bond type (bond type 1).*

Discussion

The corrected distribution

The initial search used the most general fragment showing 1,4 connectivity between sulfur and oxygen, indicated as 'type I' in Fig. 2. This fragment contains a divalent sulfur atom in an unrestricted environment. The 362 structures found in this initial search contain 806 crystallographically unique fragments with the same connectivity as the search fragment. Inspection of these structures shows that many contain multiple copies of the search fragment.

Fig. 3(*a*) shows a histogram of the sulfur–oxygen distances from the 806 fragments matching the unrestricted type-I fragment. The distribution is roughly bimodal, with one peak resulting from fragments having S⋯O distances less than 3.3 Å and the other from fragments with larger S⋯O distances. The distribution contains 383 fragments with S⋯O distances greater than 3.3 Å. A histogram of the absolute values of the torsion angle χ = O4—C3—C2—S in these fragments is also shown in Fig. 3(*a*). χ = 0° corresponds to the conformation in which the sulfur and oxygen atoms are *cis* planar. This histogram shows a trimodal distribution. Fragments show preferences for torsion-angle values of $|\chi| \approx 0, 180°$ and, to a lesser extent, 90°. The torsion-angle histo-
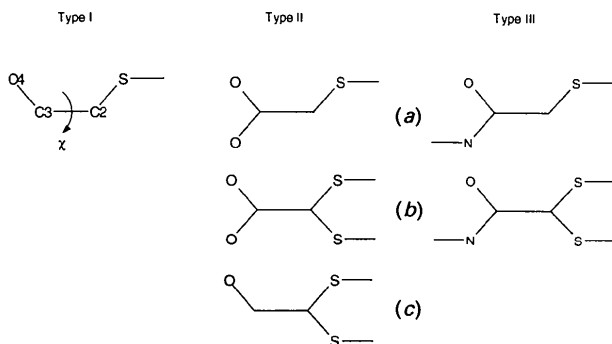

Fig. 2. Geometry of the type-I fragment (left) used in the database search for structures with general 1,4 sulfur–oxygen connectivity. The sulfur atom is divalent, and the minimum number of connections to each of the other atoms in the fragment are shown. Additional connections are permitted for the atoms other than sulfur. Bonds shown are of any type (bond type 99). To allow for unhindered rotation of the χ = O4—C3—C2—S torsion angle, the central C2—C3 bond is required to be acyclic in all search fragments used in this study. The type-II and type-III fragments are subclasses of the more general type-I fragment. All searches are corrected for the presence of type-II and type-III fragments.

gram would be flat if the χ values in these structures were randomly distributed. The fact that the histogram indicates a bias toward certain values of χ suggests the presence of an intramolecular interaction in these compounds that gives rise to the preferred torsion angles.

The average sulfur–oxygen distance for the bimodal distance distribution in Fig. 3(a) is 3.3 (4) Å. The average S···O distance observed in this search is less than would be expected if the χ values in these fragments were randomly distributed.* This finding is consistent with an intramolecular S···O interaction. Nevertheless, the question remains as to why a substantial number of fragments in Fig. 3(a) show values of χ close to 180°, giving rise to larger S···O distances.

Inspection of the compounds found in this search reveals that a number of them contain geometries of the types illustrated in Fig. 2. The type-II and type-III fragments in Fig. 2 are subclasses of the more general type-I search fragment. Structures containing type-II fragments will generate two or more competing 1,4 S···O distances in the distribution shown in Fig. 3(a). Thus, any intramolecular interaction responsible for a close S···O contact in a structure containing a type-II fragment will also result in a large S···O distance. Similarly, structures with type-III geometries yield competing 1,4 S···O and S···N distances. Typically, structures containing such fragments also display one small sulfur–nucleophile distance and one large sulfur–nucleophile distance, with associated small and large values of the torsion angle χ. In both fragment types, the larger of the two S···O distances and torsion angles are a consequence of geometric constraints, rather than the absence of an S···O interaction.

In order to account for the influence of these fragments on the distribution, a corrected population of 1,4 S···O connected fragments was created. In this population, only the smallest S···O distance and associated torsion angle in each structure containing a type-II geometry were retained. Nine structures containing type-III fragments were removed, so as not to confound the distribution of S···O contacts with competing S···N geometries. Corrected data from 149 structures containing type-II fragments were combined with data from the 204 structures containing only 'pure' type-I fragments to produce the corrected distribution shown in Fig. 3(b). The resulting histograms contain 539 fragment geometries from 353 structures. The mean S···O distance for these fragments is 3.1 (4) Å, markedly less than that of the uncorrected distribution (Fig. 3a). The

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* Using a model fragment with type-I geometry constructed from the mean bond lengths and angles found in this search, one finds the average S···O distance for a population of fragments to be 3.5 Å when the torsion angles are uniformly distributed.

torsion-angle histogram for the corrected distribution shows a much clearer preference for χ values less than 90°.

Results in Fig. 3(b) show that structures containing 1,4 S···O geometries are likely to exhibit S···O close contacts. These results indicate that a majority of fragments yielding large S···O distances and values of χ near 180° in Fig. 3(a) are the result of type-II and type-III fragments. Fig. 3(a) also shows a smaller peak in the region of $\chi = 90°$. In the corrected distribution (Fig. 3b), a number of fragments with values of χ near 90° remain. Many of these
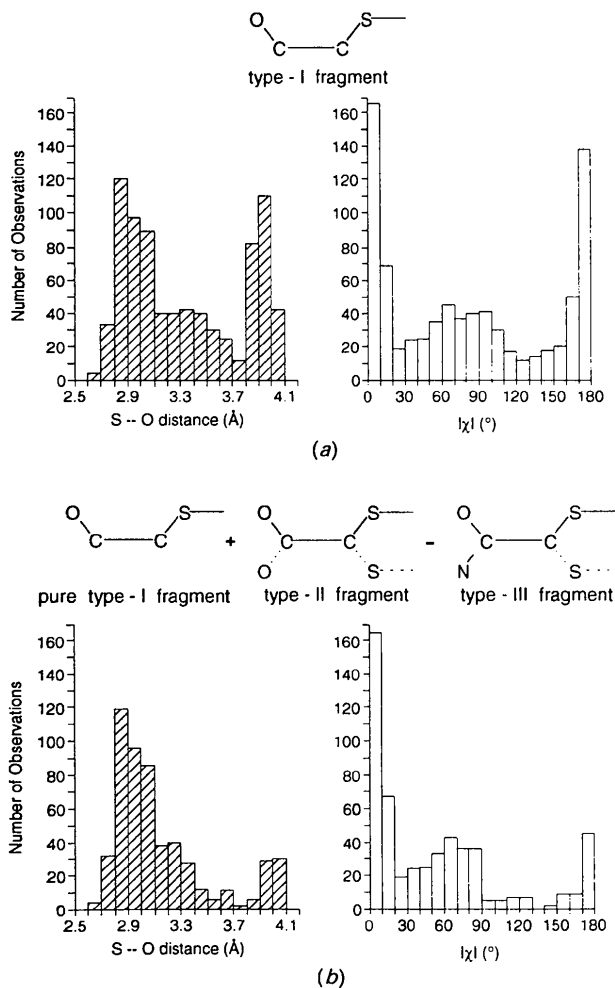
Fig. 3. (a) Uncorrected histograms of 1,4 S···O distances and $|\chi|$ = O4—C3—C2—S torsion angles found in 362 structures containing the geometry of the general type-I search fragment. (b) Histograms of 1,4 S···O distances and $|\chi| =$ O4—C3—C2—S torsion angles, corrected for the effects of structures containing type-II and type-III fragments. These histograms combine only the smallest S···O distance and associated value of χ obtained for each of the 149 structures containing type-II geometries with the data from the 204 structures containing 'pure' type-I fragments. Nine structures containing type-III fragment geometries were omitted. Dashed lines represent bonds to atoms that may be present in the search fragment.

appear to result from two competing S···O interactions in structures containing type-II geometry. For example, in a type-II(a) fragment, a sulfur atom may lie approximately equidistant between two oxygen atoms (Fig. 2).

The corrected distributions in Fig. 3(b) still show several outliers with S···O distances significantly greater than 3.3 Å and χ values greater than 90°. Examination of these outlying structures indicates that, in most cases, the sulfur atom is bound to at least one saturated carbon atom [see, for example, Riche & Pascard-Billy (1975) (refcode ZMTGOP) and Borkakoti & Palmer (1978) (refcode TMSADS10)]. Computational results predict that such structures are less likely to display close sulfur–oxygen contacts. This hypothesis is examined in the next section.
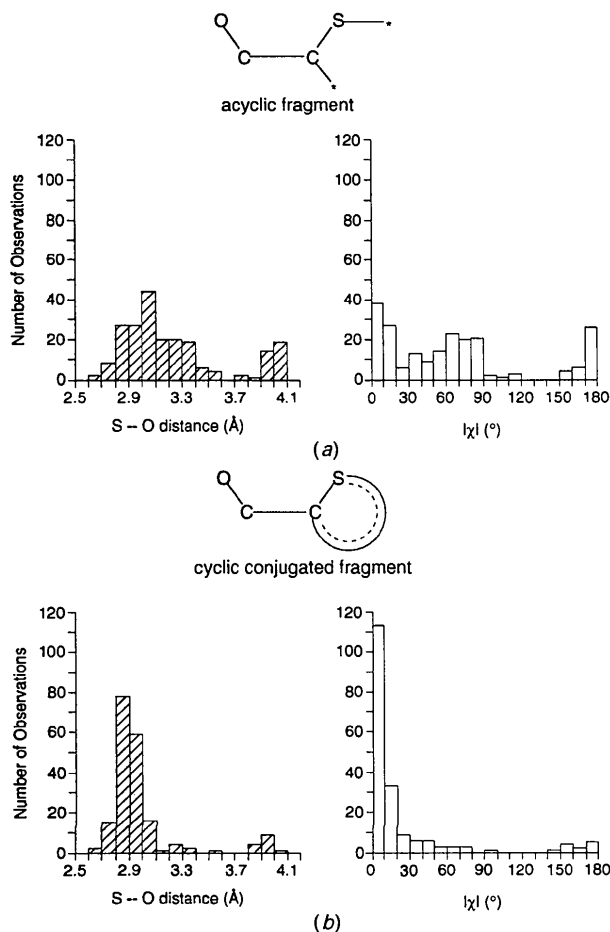

acyclic fragment

(a)

cyclic conjugated fragment

(b)

Fig. 4. (a) Histograms of 1,4 S···O distances and $|\chi|$ torsion angles for structures containing sulfur in an acyclic environment. Asterisks on the search fragment indicate that these segments are not joined. (b) Histograms of 1,4 S···O distances and $|\chi|$ torsion angles for structures containing sulfur in a cyclic conjugated environment. Both distributions are corrected for the presence of type-II and type-III fragments as in Fig. 3(b).

The influence of the sulfur environment

Computational results (Burling & Goldstein, 1992) suggest that a sulfur atom in a conjugated ring should display closer 1,4 S···O contacts than a sulfur in an unconjugated acyclic environment. These studies indicate that a sulfur atom in a conjugated cyclic environment more readily donates electron density than does a sulfur atom in an unconjugated acyclic environment. Thus, the magnitude of the positive charge is larger on sulfur atoms in cyclic conjugated systems. This results in a stronger 1,4 S···O electrostatic interaction in the cyclic conjugated system.

To test this hypothesis, the corrected distribution (Fig. 3b) was subdivided into two distributions. One distribution contains structures with the sulfur atom in an acyclic environment (Fig. 4a), the other contains structures in which the sulfur is in a ring. The torsion-angle distribution for those fragments containing sulfur atoms in cyclic systems (not shown) indicates a much clearer preference for χ values near 0° than does the distribution for acyclic sulfurs (Fig. 4a). The mean S···O distance for the cyclic fragments is 3.1 (4) Å, compared to 3.2 (4) Å for the acyclic fragments.

Most of the cyclic fragments displayed conjugation in the sulfur-containing ring. It was then necessary to determine which factor played the dominant role in producing close contacts; conjugation or the cyclic environment. Thus, the population containing sulfur in the cyclic system was searched for the conjugated fragment shown in Fig. 4(b). This fragment is conjugated at both atoms connected to the divalent sulfur atom and most nearly represents the environment of the sulfur atom in the thiazole nucleosides.* These doubly conjugated cyclic fragments show an even clearer preference for values of χ near 0° (Fig. 4b).

Results from each search are summarized in Fig. 5 and Table 1. Despite several outliers (below), we observe the closest S···O contacts in the 192 doubly conjugated cyclic systems ('cyclic conjugated'). 175 (91%) of these fragments show S···O distances less than the sum of the sulfur and oxygen van der Waals radii. The mean S···O distance in these conjugated ring systems is 3.0 (3) Å, compared to 3.3 (4) Å for compounds with saturated rings ('cyclic saturated') and 3.4 (4) Å for compounds with sulfur atoms in acyclic saturated environments ('acyclic saturated'). The S···O distances in more than 50% of the cyclic conjugated fragments lie within 0.1 Å of the median

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* A search was also performed for fragments containing doubly conjugated sulfur atoms in an acyclic environment. This search yielded only ten fragments. These had an average S···O distance of 3.1 (2) Å, with two structures having S···O distances greater than 3.3 Å. No searches were performed for either cyclic or acyclic compounds that were conjugated at only a single atom connected to the sulfur atom.

Table 1. *Summary of statistical results for all database searches described in the text (see also Fig. 5 for a graphical summary of the search results)*

Fragment type	Number of fragments	S···O distance* (Å)			$|\chi|$ (°)		
		Median	Mean	Standard deviation	Median	Mean	Standard deviation
Uncorrected (Fig. 3a)	806	3.25	3.30	0.44	76	83	65
Corrected (Fig. 3b)	539	3.02	3.15	0.37	37	54	55
Acyclic (Fig. 4a)	213	3.10	3.23	0.38	60	66	57
Cyclic	326	2.95	3.09	0.35	19	45	53
Acyclic saturated	95	3.14	3.28	0.35	67	69	55
Cyclic saturated	94	3.19	3.30	0.38	71	84	48
Acyclic conjugated	10	3.16	3.12	0.17	46	55	52
Cyclic conjugated (Fig. 4b)	192	2.90	2.99	0.29	7	24	44
Corrected (1,4 S···N) (Fig. 6)	88	3.04	3.16	0.31	8	38	48

* S···N distance for corrected 1,4 S···N-containing compounds.

(2.9 Å) of the distribution. In addition, more than 75% of these fragments display χ values less than 20°. Thus, the cyclic conjugated fragments show the tightest distributions about the smallest S···O distances and torsion angles (Fig. 4b).

Results summarized in Fig. 5 indicate that much of the spread toward larger S···O distances and χ values in the distribution of all cyclic sulfur-containing compounds is due to the presence of structures containing saturated cyclic sulfur atoms. Similarly, the spread in the corrected distribution can be primarily attributed to the presence of saturated sulfur-containing compounds, both cyclic and acyclic. The average (and median) S···O distance is nearly the same for fragments containing sulfur atoms in either acyclic saturated or cyclic saturated environments. This suggests that conjugation of the ring system, rather than the cyclic environment *per se*, gives rise to the close S···O contacts.

The distribution of fragments containing doubly conjugated cyclic sulfurs (Fig. 4b) does contain 17 outlying structures. These fragments show S···O distances greater than 3.3 Å, and large values of χ. Based solely on the computational results, these outliers are unexpected. However, a closer examination

of these structures reveals that, in 13 of the 17 outliers, S···O close contacts are likely to be prevented by competing intermolecular or intramolecular interactions.* However, the intramolecular S···O interaction predominates in the great majority of conjugated cyclic structures, despite the presence of intermolecular packing forces and other competing interactions.

Sulfur–nitrogen contacts

Computational results (Burling & Goldstein, 1992) suggest that 1,4 S···O contacts of the type described above are electrostatic in origin, resulting from an

* Among these competing interactions are: (1) intramolecular hydrogen bonding (refcodes ACCTHP, JECMIN, VEMCUL); (2) intermolecular hydrogen bonding (FABSOQ10); (3) competing 1,4 and 1,5 S···O interactions (SAFZOO, HETERB, THMPSH10, VEMCUL); (4) competing 1,4 S···N''' interactions (DETFIR); (5) competition from three conjugated sulfur-containing rings for the same oxygen atom (VAVSOA); and (6) unfavorable steric interactions (BIMAZT, FUHHUL, FUHJIB, GIKJOZ, THMPSH10). In three of the four remaining outlying structures (DIBSUC, DILLAL, FODJAJ), large thermal parameters and/or disorder in several thiophene moieties suggest potential misidentification of the thiophene sulfur. We cannot account for the larger S···O distance in one compound (THDSER).
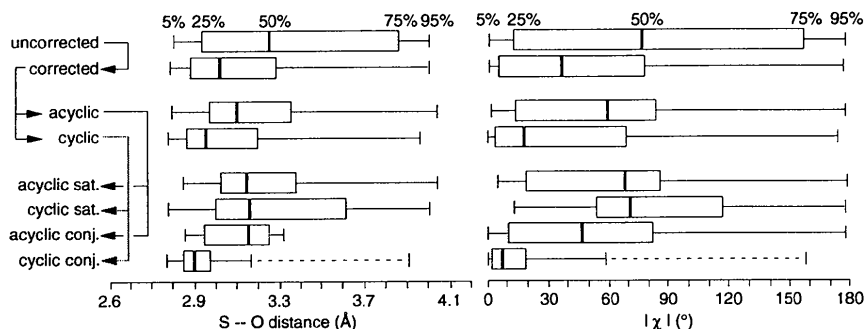

Fig. 5. Summary of the distributions of 1,4 S···O distances and $|\chi|$ torsion angles from each search described in the text ('sat.' = saturated and 'conj.' = conjugated). Arrows indicate subpopulations of a particular search. For example, the cyclic saturated and cyclic conjugated structures are a subset of the population of cyclic compounds. Each rectangle encloses the middle 50% of the data from a given search. The heavy vertical line indicates the median of the data. Lines extending from each rectangle mark the 5th and 95th percentiles of the distribution. The dashed lines in the cyclic conjugated results indicate the extent of the distribution if the 13 outlying structures discussed in the text are included.

attractive interaction between an electrophilic sulfur atom and a nucleophilic oxygen atom. Thus, close 1,4 contacts would be expected between sulfur and other nucleophiles as well. In order to investigate this hypothesis, the database was searched for structures containing 1,4 connected divalent sulfur and nitrogen atoms. This search yielded 78 structures, 69% of which contained fragments having S···N distances less than 3.3 Å. Fig. 6 shows corrected histograms of S···N distances and associated torsion angles, analogous to those shown in Fig. 2(b). The results of this search are similar to those for the 1,4 S···O-connected structures. These data support the hypothesis that an attractive electrostatic interaction is responsible for general sulfur–nucleophile 1,4 close contacts. Additional searches are now underway to examine compounds containing fragments of the type sulfur–X–X–nucleophile, where X is any atom, as well as fragments containing selenium–nucleophile contacts. These studies will further investigate the generality of the nonbonded electrophile–nucleophile interaction.

Summary

A search of the crystallographic database shows that intramolecular 1,4 S···O and S···N close contacts are common. Divalent sulfur atoms that are part of a ring form closer 1,4 S···O contacts than do acyclic divalent sulfurs. Structures with divalent sulfur atoms in conjugated ring environments are more likely to exhibit close intramolecular 1,4 contacts than structures with sulfur atoms in either saturated cyclic or acyclic systems. Earlier theoretical work, which suggests that conjugated ring systems yield stronger attractive electrostatic S···O interactions (Burling & Goldstein, 1992), is consistent with these results. These findings suggest that 1,4 sulfur–nucleophile attractions are an important class of nonbonded intramolecular interactions.

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pure
1,4 S -- N
type - I fragment

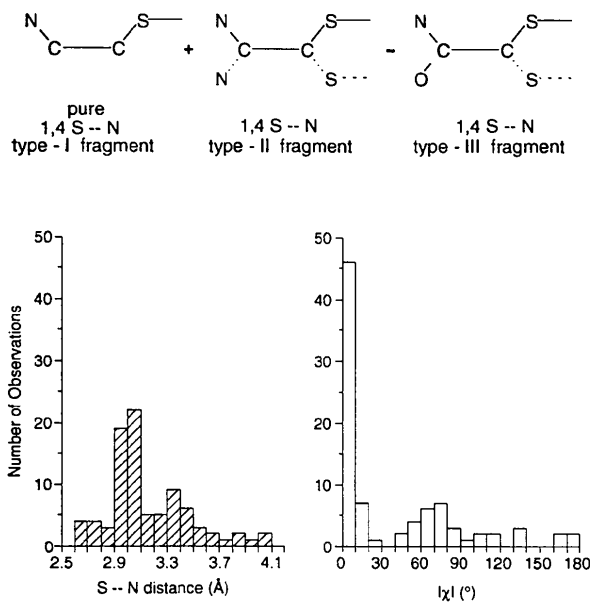1,4 S -- N
type - II fragment

1,4 S -- N
type - III fragment

Fig. 6. Histograms of 1,4 S···N distances and |χ| torsion angles for structures containing divalent sulfur and nitrogen atoms. The distributions are corrected for the presence of nitrogen-containing type-II and type-III fragments as in Fig. 3(b).