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Statistical Analysis of Noncovalent Interactions of Anion Groups in Crystal Structures. I. Hydrogen Bonding of Sulfate Anions

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Abstract

The hydrogen-bond acceptor characteristics of sulfate dianions are analyzed in crystal structures of small molecules. For 85 anions, neither coordinated to metal ions nor covalently bonded, 697 hydrogen bonds are found. Of these, 266 (38%) are the O···H—O type and 431 (62%) are the O···H—N type, proportions that correspond well to the stoichiometry of the compounds studied and indicate no preference for a particular donor. The analysis of the data set, after classifying the hydrogen bonds according to the different types of donors, shows that O···H—O bonds are more linear than O···H—N. The anion oxygen–acceptor function is characterized by multiple hydrogen bonding. Only in 56 cases does a sulfate oxygen participate in a single hydrogen bond. In most cases every sulfate oxygen is coordinated by two (187 cases) or three (89 cases) hydrogen bonds. For three H donors, the preferred coordination geometry of the sulfate oxygen is pyramidal. The most frequent coordination around a sulfate dianion is with eight to ten H donors. Thus, sulfate dianions can play a significant cohesive role in molecular aggregation.

1. Introduction

Studies of charged species (cations and anions) have become an active research area in organic chemistry and biology. Their role as structural agents is important in molecular association processes and in mediating the tertiary structures of proteins and nucleic acids. Whereas much information has been collected for cations in small-molecule and macromolecular crystal structures, work on anionic environments has received little attention. However, knowledge of anionic complexation can be crucial to our understanding of the interactions between protein residues, proteins and substrates, and proteins and nucleic acids. To describe the recognition of an anionic group by its environment requires a knowledge of its binding stereochemistry. Anions bind through electrostatic interactions and, in biological media, mostly by hydrogen bonding. Their targets are essentially H donors and positively charged species (*e.g.* N^+).

In this work we are concerned with anions involved in macromolecular interactions. Earlier surveys studied the environment of sulfonyl and phosphonyl groups (Alexander, Kanyo, Chirlian & Christianson, 1990; Kanyo & Christianson, 1991) and in 1993 a study of sulfate binding with proteins was published (Chakrabarti, 1993) *via* a survey of the Brookhaven Protein Data Bank. Recently, a database study of hydrogen bonding for carboxylates, sulfonates and monohydrogen phosphonates with NH_2 groups was published (Pirard, Baudoux & Durant, 1995).

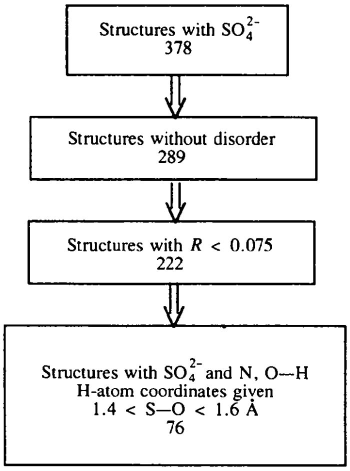
Our purpose is to systematically analyze the environment of a given anion in the hope of deriving precise and reliable stereochemical descriptions of its binding, using the Cambridge Structural Database (CSD: Allen, Kennard & Taylor, 1983). Indeed, the systematic study of small-molecule crystal structures, where the existing interactions are similar to those in biological systems, allows precise measurements of bond lengths and angles that typify the behavior of the anion under study.

We wish to answer the following questions: (*a*) What is the most frequent binding mode? (*b*) Is there a preferred H donor? (*c*) Are there characteristic ranges (most preferable values) for the geometrical parameters defining the bond? (*d*) Is there a particular spatial distribution of the donors around the anion?

As we wanted our results to be relevant to biological systems, we restricted the H donors (*D*) to oxygen (O) and nitrogen (N). Possible O···H—C interactions were not taken into account. We also considered only those crystal structures in which the anion neither binds covalently nor coordinates to metal cations. We present here the first part of our work, a study of hydrogen bonding to sulfate dianions, SO_4^{2-}.

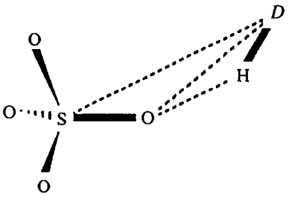
2. Methods

X-ray and neutron crystal structures of small molecules were retrieved from the CSD (Version 5.8, 1994; Allen *et al.*, 1991). The selection of structures was made as shown in Scheme I.



Scheme I.

Only those structures containing one or more potential intermolecular hydrogen-bond donor (N or O) were considered. The 2D (two-dimensional) substructure searches and 3D geometrical searches were carried out using the *QUEST3D* (Cambridge Structural Database, 1992) program. The resulting subfile of data contained 76 crystal structures with 85 observed anions (Table 1). Evaluation with *GSTAT* was carried out using the following geometrical parameters: the distances $S\cdots D$, $O\cdots D$ and $O\cdots H$, and the angles $<(OHD)$, $<(SOD)$ and $<(SOH)$ for the probe fragment illustrated in Scheme II.



Scheme II.

The geometrical criteria which are selected to characterize hydrogen bonding have been the subject of some discussion (Taylor, Kennard & Versichel, 1983, 1984; Taylor & Kennard, 1983; Jeffrey & Maluszynska, 1990; Görbitz & Etter, 1992; Steiner & Saenger, 1992; Llamas-Saiz, Foces-Foces, Mo, Yanez & Elguero, 1992). There are two distinct viewpoints. In the first, an acceptor to donor ($A\cdots D$: A, $D = O$, N) distance of less than 3.2 Å is used and longer separations are referred to as van der Waals interactions, while in the second approach a longer threshold is used. In this study the primary selection of $O\cdots H—D$ bonds was carried out with more liberal criteria: $O\cdots D < 3.6$ Å and angles of $90 < (OHD) < 180°$. It appears that selected $O\cdots D$ distances are distributed in two domains: $2.5 < O\cdots D < 3.2$ Å and $3.2 < O\cdots D < 3.6$ Å. Considering that $O\cdots D$ distances less than 3.2 Å correspond to hydrogen bonding we used a final $O\cdots D$ cut-off of 3.2 Å and angle $90 < (OHD) < 180°$. The coordinates of the H atoms were normalized (Taylor & Kennard, 1984). Multiple occurrences of a functional group within any entry were considered since they display independent parameters. If a particular crystal structure had more than one entry in the database, only the best and/or most recent analysis was accepted. Additionally, the geometry of hydrogen bonding was also examined individually using the graphics programs *PLUTO* (Motherwell & Clegg, 1978) and *SGR3M* (written by Claude Riche of this laboratory). Statistical descriptors are defined and described by Snedecor & Cochran (1989). The results are represented as histograms and scatterplots using KaleidaGraph (1990) and *MolView* (Cense, 1992).

3. Hydrogen-bond geometry

The 76 retrieved crystal structures are chemically highly heterogeneous, comprising both organic (42 structures) and organometallic (34 structures) compounds. Most (78%) are hydrates (45 structures) or have hydroxy groups (12 structures). Out of 76 structures 28 contain a single type of donor: 10 with oxygen and 18 with nitrogen. The remaining 48 structures contain both donors (O and N). We identified 329 O—H donors (136 water molecules, 15 N—OH fragments and 42 C—OH groups) and 510 N—H donors. All N donors are either charged or participate in a delocalized system. More than 80% of the potential donors bind with sulfate. We identified 697 hydrogen bonds: 266 (38%) are the $O\cdots H—O$ type and 431 (62%) are the $O\cdots H—N$ type. No preference for hydrogen bonding of sulfate with oxygen or nitrogen donors was observed: the proportion of potential O—H (35%) and N—H (65%) donors corresponds to the proportion of observed hydrogen bonds. In a first approach these two hydrogen-bonding groups were treated together.

3.1. *Composite results for N and O donors*

Fig. 1 and Table 1 present univariate statistics for all hydrogen-bond data ($D = N$ and/or O). The $S\cdots D$ distances range from 3.372 to 4.529 Å [mean = 3.785 (7) Å] with the bell-shaped distribution close to normal. The $O\cdots D$ distances are in the 2.443–3.180 Å range [mean = 2.838 (5) Å] with a flat-topped (negative kurtosis) and slightly nonsymmetrical distribution (skewness 0.22). The $O\cdots H$ distance distribution [from 1.47 to 2.59 Å, mean = 1.991 (7) Å] is nonsymmetrical, having a small tail to the right of 2.2 Å (skewness 1.6). For the angle at oxygen $<(SOD)$ [range 87.8–176.2°, mean = 120.7 (5)°], the most favorable domain is in the 100–130° range. Only 20 (3%) of the angles occur in the 150–180° range. The angles at oxygen $<(SOH)$ (range 71–173°) show a

Table 1. *Statistical results for the geometry of the hydrogen bonding*

CSD refcodes: ADENSL, ADESUL, ADHCOS10, AGLYSL01, AMADCS, AMPCUS, AZADMS10, BGDUSM10, BINWUQ, BOLPUN, BUMDOC, CBHYZS, CEJVAO, CIMNAN, COETDS10, COVKUT, CUJCOZ, CUPBAQ, CUPJEC, CUPJEC01, CURHIG, DAJNOR01, DAPRSM, DAPXEX, DGLSLM10, DHYZAS01, DIZXAL, DULVEL, EBGAGS, FEBYEQ, FIZHUR, FIZJAZ10, GAWTED, GAWTED01, GILBUY, GLYMOS, GLYZNS10, GUALSU10, GUCRSU, HACDEU, HGUANS, HPPAES, IGUSUH10, IMDZSD, JENBAF, JUKWAN, JURZAX, KNMYSL, KOFCUD, LAGDIG, LUPCGS, MALAMS10, NETRSN, NIDTSS10, OXENOS, OXMPDS, OXOXPD, PTUCUS10, SEZGOT, SOPNIU, SOPPOC, TAENNI01, TAHYPC, TAPTAF, TCHYZS, TCHZCU, TENNIS01, TGLYSU20, TSCUSL, URCASU, VANCAO, VOGTIU, WAHWIL, YAPGIF, ZZZTRE01.

	S···*D* (Å)			O···*D* (Å)			O···H (Å)		
	D=N/O	*D*=N	*D*=O	*D*=N/O	*D*=N	*D*=O	*D*=N/O	*D*=N	*D*=O
Minimum	3.372	3.372	3.400	2.443	2.616	2.443	1.466	1.466	1.562
Maximum	4.529	4.462	4.529	3.180	3.180	3.119	2.591	2.587	2.591
Mean	3.785	3.809	3.745	2.838	2.894	2.747	1.991	2.030	1.929
Median	3.749	3.775	3.722	2.827	2.890	2.744	1.971	1.996	1.911
R.m.s.	3.789	3.815	3.749	2.840	2.900	2.749	2.001	2.040	1.937
SD	0.198	0.202	0.183	0.133	0.117	0.105	0.196	0.200	0.173
Variance	0.039	0.041	0.033	0.017	0.016	0.011	0.038	0.040	0.029
SE	0.007	0.010	0.011	0.005	0.006	0.006	0.007	0.010	0.010
Skewness	0.823	0.668	1.184	0.216	0.210	0.469	0.622	0.480	0.850
Kurtosis	0.924	0.361	2.608	−0.349	−0.478	0.740	0.331	−0.03	1.603
Number	697	431	266	697	431	266	697	431	266

	<(SO*D*) (°)			<(SOH) (°)			<(OH*D*) (°)		
	D=N/O	*D*=N	*D*=O	*D*=N/O	*D*=N	*D*=O	*D*=N/O	*D*=N	*D*=O
Minimum	87.8	87.8	92.8	70.5	74.3	70.5	100.6	100.67	102.3
Maximum	176.2	176.2	172.2	173.2	173.2	165.9	179.1	178.9	179.2
Mean	120.7	119.1	123.2	118.1	116.7	119.6	159.9	157.6	163.8
Median	119.3	117.4	122.0	118.6	116.8	117.7	163.9	161.0	167.8
R.m.s.	121.5	119.9	123.9	119.3	117.7	120.3	159.9	158.4	164.4
SD	13.6	14.1	12.4	14.6	15.7	13.1	15.1	15.8	13.2
Variance	185.7	198.8	154.7	214.1	246.8	172.2	230.1	249.9	174.8
SE	0.51	0.68	0.76	0.55	0.81	0.72	0.57	0.76	0.81
Skewness	0.97	0.89	1.40	−0.19	0.16	−0.69	−1.45	−1.22	−2.03
Kurtosis	2.02	1.33	3.92	1.39	0.90	2.62	21.4	1.38	4.93
Number	697	431	266	697	431	266	697	431	266

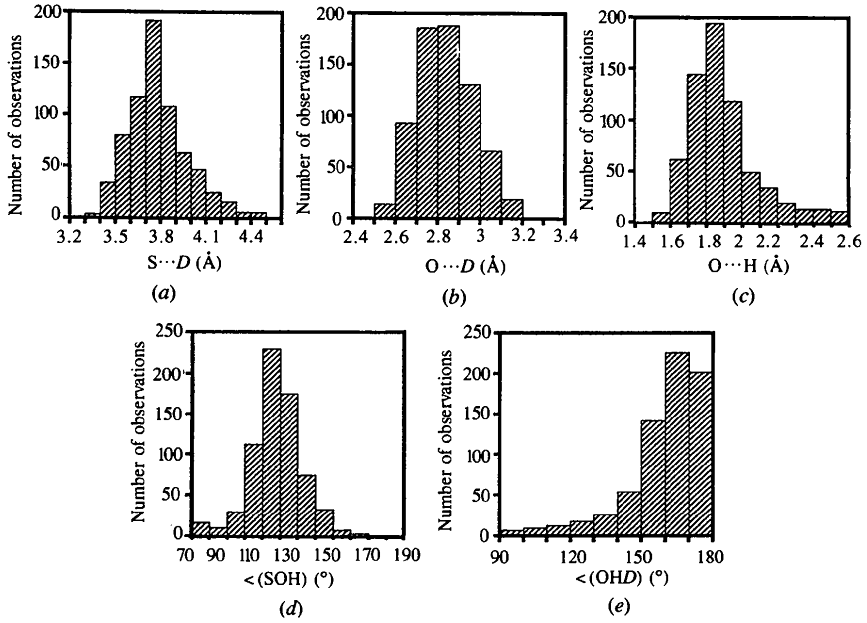


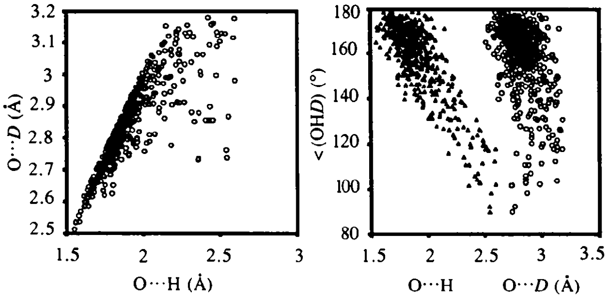
Fig. 1. Histograms for the S—O···H—*D* fragment (all hydrogen bonds merged). (*a*) S···*D*, (*b*) O···*D*, (*c*) O···H, (*d*) <(SOH) and (*e*) <(OH*D*).

near-normal distribution with a maximum at 120°. The distribution for the < (OH*D*) angle rises to a maximum around 160–180° [mean = 160.0(6)°].

Bivariate correlations were also calculated from all combinations of parameters. The best correlation ($r = 0.85$) is observed for the distance S···*D* with bond angle < (SO*D*), which has obvious geometrical relations. Good correlations are realized between the distances O···*D* and O···H ($r = 0.81$) and between the distance O···H and the bond angle at H ($r = -0.84$, Figs. 2*a* and *b*). It is clear that the stronger bonds tend to be linear.

3.2. *Individual results for N and O donors*

Fig. 3 shows the histograms for important parameters after classifying the hydrogen bonds according to the different types of donors – O and N. Summary statistics are included in Table 1.



(*a*) (*b*)

Fig. 2. Correlations of geometrical parameters (all hydrogen bonds merged). (*a*) Plot of O···H *versus* O···*D*; (*b*) plot of O···H and O···*D* *versus* <(OH*D*).

Hydrogen bonds to O—H donors [means: $O^- \cdots O = 2.747(6)$, $O^- \cdots H = 1.93(1)$ Å] are shorter and stronger than bonds to N—H donors [means: $O^- \cdots N = 2.894(6)$, $O^- \cdots H = 2.03(1)$ Å]. These results can be correlated with the smaller spread of data values for O—H donors, for example, 94% of the O···HO bonds lie between 1.60 and 2.20 Å and the same quantity of O···HN bonds lie between 1.70 and 2.50 Å. The angles at H exhibit the same correlation with 80% of the O—H*D* angle between 160 and 180° for O donors, and between 145 and 180° for N donors. The potential functions calculated by Gavezzotti & Filippini (1994) for carboxylic acids and amides agree with these strength differences.

Bivariate correlations were also calculated for all combinations of parameters. These relationships are similar for both O and N donors.

4. Hydrogen coordination

We now consider the different types of hydrogen bonding: (*a*) two-center, (*b*) three-center or (*c*) four-center bonds (Scheme III).

Type (*d*) illustrates the three-center case where a donor is facing two oxygens of the same sulfate at one time. This bonding mode was found for 18 fragments with *D*═N and five with *D*═O. The binding mode (*e*) was found in only three structures and these were not studied further.

It is clear from Scheme II that, for equivalent three- or four-center bonds (cases *b* and *c*), the angle at H will

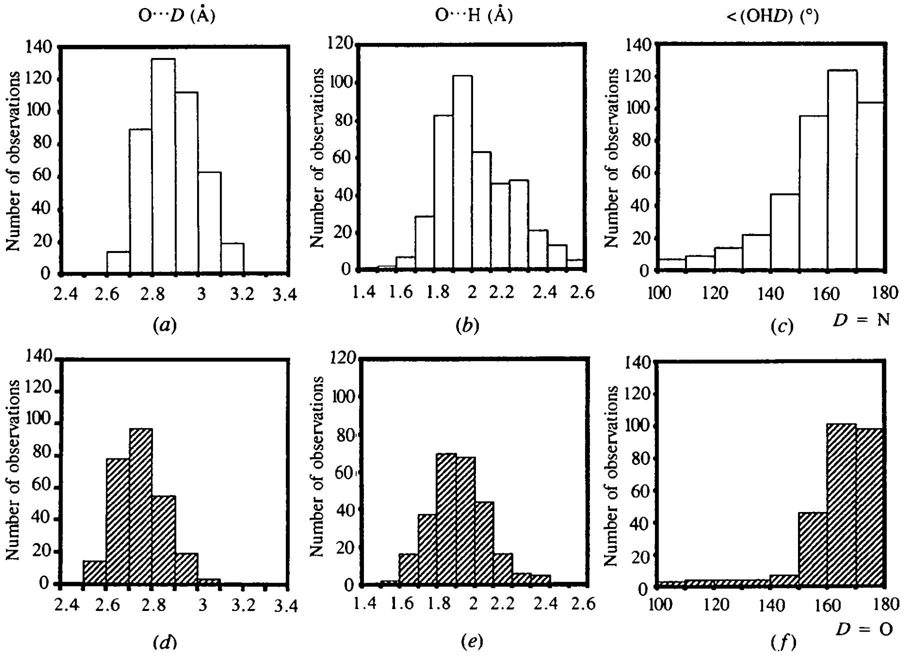
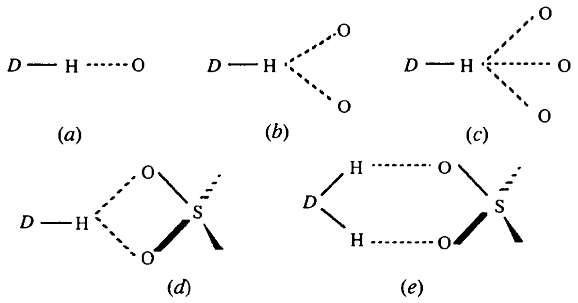


Fig. 3. Univariate statistics for different types of hydrogen bonds: white graphs correspond to N donors and shaded to O donors. Histograms for the O···H—*D* fragment: (*a*) and (*d*) show O···*D*, (*b*) and (*e*) show O···H, and (*c*) and (*f*) show <(SOH).



Scheme III.

be much less than 160°. On the graph showing the distribution of the value of <(OH*D*) when *D* is a nitrogen, there is a long tail to the left of 160° (Fig. 3*c*). This tail is practically absent in the histogram of *D* = O (Fig. 3*f*). This feature is also observed in Fig. 2(*b*), which is a plot of <(OH*D*) *versus* O· · ·H distances. We can deduce, then, that O· · ·H—O bonds are closer to linearity, whereas with nitrogen we often encounter the hydrogen-bond types (*d*) and (*b*) shown in Scheme III, which correspond to a chelated three-center bond and a bifurcated three-center bond, respectively (Jeffrey & Saenger, 1991). We selected one example of a structure having different primary modes of H coordination (Fig. 4). The structure of L-lysine sulfate contains all types of hydrogen bonding, namely two-, three- and the rarer four-center bonds.

5. Oxygen coordination by hydrogen bonds

For strong hydrogen bonds, the directionality of *D*—H· · ·O, that is the preference of the *D*—H vector to point towards the lone-pair direction of the O atom, has been found to depend on whether the O atom is sp^2 or sp^3 hybridized (Taylor, Kennard & Versichel, 1983; Murray-Rust & Glusker, 1984; Görbitz & Etter, 1992).

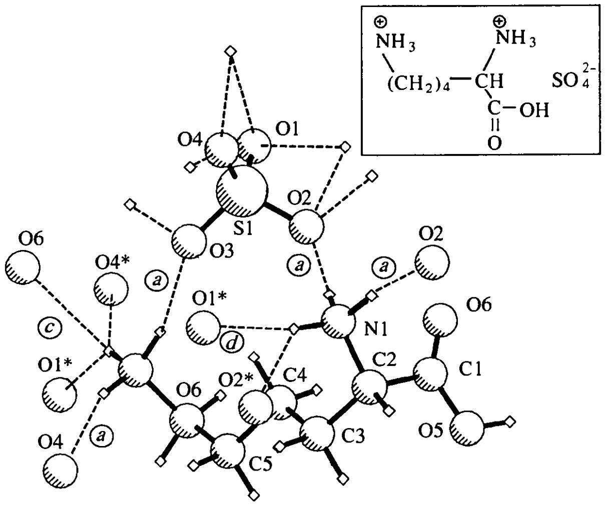
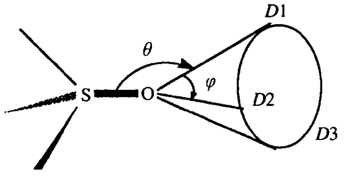


Fig. 4. *PLUTO* (Motherwell & Clegg, 1978) diagram illustrating the different types of hydrogen bonding (see Scheme III): (*a*) two-center, (*d*) three-center and (*c*) four-center bonds in the structure BOLPUM. The hydrogen bonds are shown by dashed lines. Atoms marked by an asterisk belong to the same SO_4^{2-}.

The plot of <(SOH) angles *versus* O· · ·H distances (Fig. 5) shows a clear preference for the hydrogen bond to lie in a specific direction, that which has the (SOH) angle at 120°. This feature is illustrated further in Fig. 6, which is a scatterplot of H-donor positions around the sulfate oxygen.

The environment of the sulfate oxygen can be represented by Scheme IV, where θ and φ are <(SO*D*) and <(*D*1· · ·O· · ·*D*2), respectively. In order to analyze the environment of the sulfate ion we classified all hydrogen bonds according to the number which coordinated each sulfate oxygen (Scheme V). A sulfate oxygen participates in a unique hydrogen bond in only 56 cases (*D* = N in 32 cases and *D* = O in 24



Scheme IV.

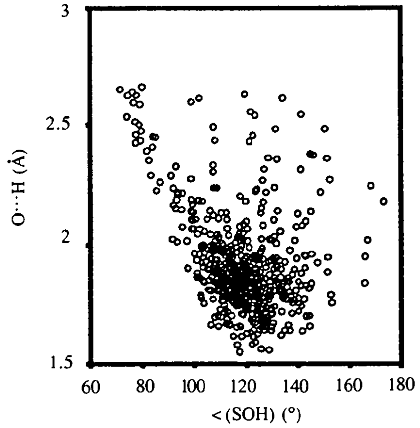


Fig. 5. Scatterplot of <(SOH) angles *versus* O· · ·H distances.

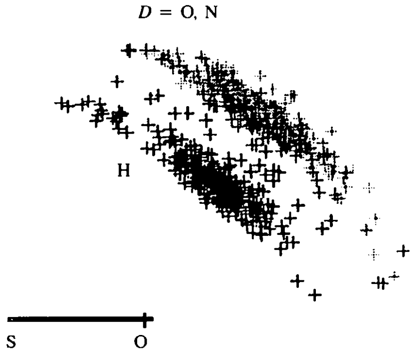
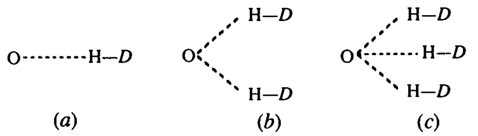


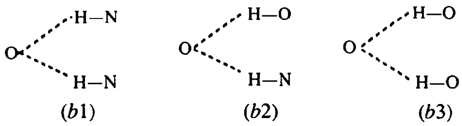
Fig. 6. Distribution of H-donor atoms around S—O. The outside crescent: N and O donors, inside crescent: H atoms.

cases). In most cases, a sulfate oxygen binds twice (187 cases) or three times (89 cases). Hence, the proportions of hydrogen bonding of types (*a*):(*b*):(*c*) is 3:10:5, respectively.

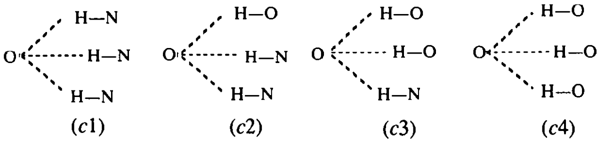


Scheme V.

When a sulfate oxygen is involved in a type (*b*) hydrogen bond, there are three possible bonding modes (Scheme VI). We found that hydrogen bonding of type (*b*1), (*b*2) and (*b*3) is observed 83, 54 and 50 times, respectively. Hydrogen bonding of type (*c*) gives rise to four combinations (*c*1–*c*4, Scheme VII), which are observed in 37, 27, 14 and 11 cases, respectively.



Scheme VI.



Scheme VII.

We observed that the geometrical parameters for hydrogen bonding of a certain type (*a*, *b* or *c*) exhibit the same distributions as those for all data merged together.

In cases of multiple bonding (types *b* and *c*) the $D1\cdots O\cdots D2$ angle was calculated (Fig. 7). For hydrogen bonding of type (*c*), the three donor atoms occur on the surface of a cone around the sulfate oxygen, forming a distorted tetrahedron with $70 < \varphi < 100°$. For hydrogen bonding of type (*b*), two modes are observed: the first corresponds to a coplanar arrangement of $D1$ and $D2$ with S—O, while the second is similar to the disposition in type (*c*). In this latter case two donors occur at the apices of a virtual tetrahedron with the third position either vacant or occupied by an atom vicinal to the donor group.

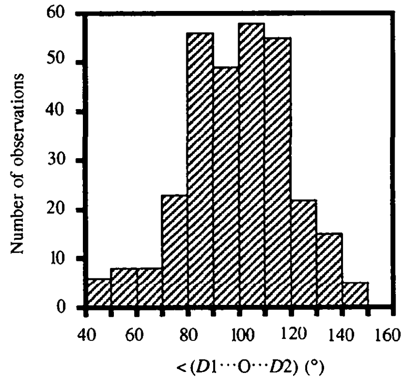


Fig. 7. Multiple binding. Angular distribution $D^1\cdots O\cdots D^2$ (Scheme IV) at a sulfate oxygen bonded twice or three times (Scheme V).

Finally, we considered the total number of hydrogen bonds around each sulfate. The histogram (Fig. 8) shows the frequency of these hydrogen-bond coordination numbers: 8–10 coordination occurs most frequently, which means that each oxygen is bonded twice or three times to a donor.

6. Typical examples of sulfate hydrogen bonding

A few selected examples will be illustrated. These do not necessarily correspond to the average geometrical situations discussed in the statistical analysis above, but are based on simplicity and typicality criteria. Fig. 9

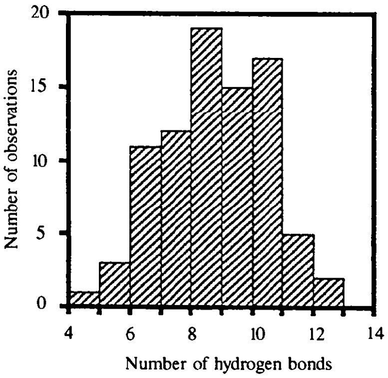


Fig. 8. Anion–acceptor function of the sulfate: frequency of hydrogen-bond coordination members.

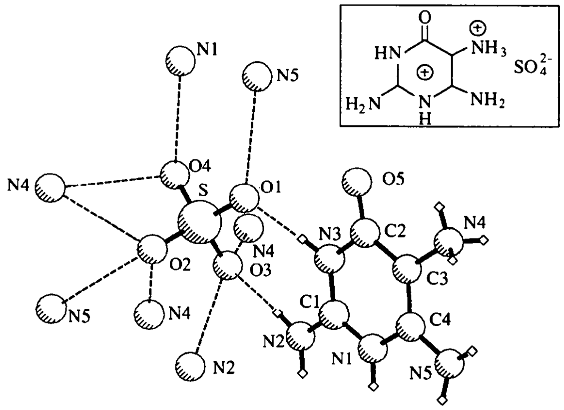


Fig. 9. Typical example of multiple hydrogen bonding of sulfate. *PLUTO* (Motherwell & Clegg, 1978) diagram illustrating the environment of SO_4^{2-} in the structure HACDEU. The sulfate oxygen participates in two (O1 and O4) and three (O2 and O3) hydrogen bonds. Geometrical arrangement of the donor around oxygens: at O2 and O3 – pyramid; at O1 – coplanar; at O4 – noncoplanar with S—O$^-$ bond. The hydrogen bonds are shown by dashed lines.

clearly shows that all sulfate oxygens in 5-ammonium-6-amino-isocytosinium sulfate are involved in multiple hydrogen bonding. The O2 and O3 atoms are each bound to three nitrogen H donors, which form a pyramid around both oxygens. Two other O atoms are bound twice but differently, the donors being coplanar with S—O$^-$ at O1 and pyramidal at O4. This example also illustrates the case where a donor is facing two oxygens of the same sulfate at one time (Scheme III, type *d*).

In all structures retrieved and carefully examined (most were displayed on the screen), the only hydrogen-bond donors are charged N$^+$ and OH groups (if present). All the relevant groups utilize their maximum hydrogen-bonding potential. When available, water molecules complete the coordination sphere of the anion as much as possible, allowing the highest coordination number to be attained (Fig. 10). Here the water molecule binds with two oxygens of the same sulfate at one time (Scheme III, type *d*).

All the information on hydrogen-bond interactions is summarized in a graphic presentation of superimposed fragments (Fig. 11). The distribution of points is not isotropic and shows that hydrogen binding occurs preferentially in certain directions.

7. Conclusions

Our observations can be summarized as follows:

(i) The results underline the extraordinarily active character of the sulfate for hydrogen bonding. The sulfate dianion can link to each possible H donor.

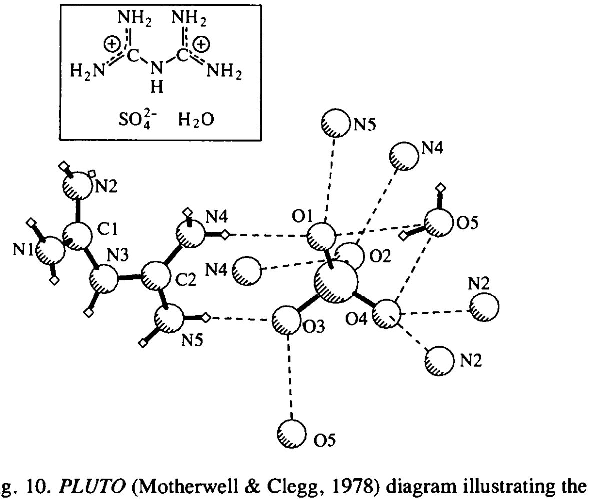


Fig. 10. *PLUTO* (Motherwell & Clegg, 1978) diagram illustrating the environment of SO_4^{2-} in the structure BGDUSM10. The anion oxygen–acceptor function is characterized by multiple hydrogen bonding. The sulfate oxygen participates in two (O2 and O3) and three (O1 and O4) hydrogen bonds. Geometrical arrangement around oxygens: at O1 and O4 – pyramidal; at O2 – noncoplanar; at O3 – coplanar. The water molecule binds with two oxygens of the same sulfate at one time (Scheme III, type *d*). The hydrogen bonds are shown by dashed lines.

(ii) The sulfate dianion makes short and directional hydrogen bonds, as shown by the observed ranges for angles and distances.

(iii) There is no preference for hydrogen bonding of sulfate with O or N donors: the proportion of potential O—H and N—H donors corresponds to the proportion of observed O···H—O and O···H—N hydrogen-bond types.

(iv) The most striking result is the high number of hydrogen bonds to the sulfate, which results in the sulfate being surrounded by a cloud of hydrogen donors. This multiple binding (two or three) of each oxygen implies that the tetrahedral sulfate will gather around itself a maximized three-dimensional environment of donors at close contact distances. The anionic oxygen exhibits a preferred pyramidal stereochemistry.

The high percentate of hydrates (78%) observed in the number of retrieved structures allows completion of the sulfate coordination. When the number of molecular H donors is not sufficient (or the packing is subject to steric problems), water molecules will complete the binding sphere around each oxygen.

Consequently, the sulfate anion will behave as a steric 'tightener', placing the attracted partners in close contact. A very good example is offered by sulfate-binding protein (Pflugrath & Quioccho, 1988), where a sulfate anion is hydrogen-bonded seven times to three peptide helices which diverge from the sequestered anion. Chakrabarti (1993) has already noted that among the 41 sulfate fragments retrieved from the Brookhaven Data Bank, 17 were bound to different macromolecules, symmetrically related or not. Chakrabarti also noted the high number of close contacts (7 + 5) around the sulfate, but could not distinguish the hydrogen bonds from pure steric contacts.

The choice of salts in protein crystallogenesis is important with regard to both the type of anion and the type of cation. Due to its small size and its ability to become surrounded very closely and strongly by H donors, the sulfate anion can play a very important role as a water molecule linker.

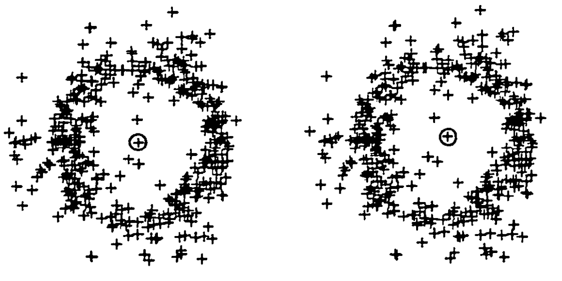


Fig. 11. Stereodiagram of the distribution of donor groups around sulfate. The giant molecule (all fragments superimposed) is projected along the S—O bond (S and O superimposed).

The short and directional hydrogen bonds centered on the sulfate anion induce rigidity to the molecular association due to this anionic link.

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