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# Hydrogen Bonds Involving Sulfur Atoms in Proteins

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***ABSTRACT*** **Intrachain hydrogen bonds are a hallmark of globular proteins. Traditionally, these involve oxygen and nitrogen atoms. The electronic structure of sulfur is compatible with hydrogen bond formation as well. We surveyed a set of 85 high-resolution protein structures in order to evaluate the prevalence and geometry of sulfur-containing hydrogen bonds. This information should be of interest to experimentalists and theoreticians interested in protein structure and protein engineering.**

**Key words: protein structure, hydrogen bonding, interactions of side chains, cysteine, methionine, half-cystine**

## INTRODUCTION

Sulfur is found in proteins in the side chains of the amino acids cysteine and methionine. Cysteine is best known for its unique ability to form cross-links via disulfide bonds. Methionine is usually categorized as an uncommon hydrophobic amino acid. Although a thorough analysis of metal ion binding by these amino acids in proteins has recently been completed,[1] little attention has been given to their ability to participate in hydrogen bonding[2] perhaps because of their relative scarcity in proteins of determined three-dimensional structure. Gray and Matthews[3] have called attention to the role of side chain–backbone hydrogen bonds in helices. We were motivated to survey the frequency and geometry of sulfur-containing hydrogen bonds in globular proteins in order to better assess the importance of this interaction and gauge the interatomic packing interactions of sulfur. Site-directed mutagenesis has made it easy to exchange amino acids in a protein. Methods for predicting the effects of various amino acid substitutions on protein structure and function are important for experimental design. A more detailed examination of the interactions particular to specific amino acids should help reach this end.

Reduced sulfur atoms are known on sound theoretical basis to be capable of accepting or donating hydrogen bonds.[4] The sulfhydryl group of cysteine can act either as a hydrogen bond donor or as an acceptor. The sulfurs of methionine and half-cystine, lacking hydrogens, can only accept hydrogen bonds. The strength of a hydrogen bond between $H_2S$ and $H_2O$ has been calculated to be 3.1 to 3.2 kcal/mol in vacuo when sulfur is the hydrogen bond donor or acceptor.[4] In noncovalent enzyme–substrate interactions, the magnitude has been shown experimentally to be slightly smaller: upon replacing a cysteine involved in substrate binding by glycine and serine, Wilkinson and co-workers calculate the decrease in transition state stabilization to be approximately 1.1 kcal/mol.[5] The strength of *structural* hydrogen bonds in proteins has not been probed experimentally, but it is presumed to be of similar magnitude.

Hydrogen bonds involving sulfur atoms are longer than those involving nitrogen or oxygen because of sulfur's larger size and more diffuse electron cloud. The equilibrium distance from donor to acceptor atom in a hydrogen bond between a hydroxyl group and an oxygen atom is 2.95 Å, whereas the distance between a sulfhydryl group and an oxygen is 3.66 Å.[4] The distance between -SH and O in crystals of L-cysteine is 3.4 Å.[6]

Sulfur is instrumental in the active sites of the sulfhydryl proteases such as papain and actinidin[7] and in the viral cysteine proteases.[8] These enzymes use Sγ of cysteine as a nucleophile for peptide bond cleavage. McGrath et al.[9] recently substituted serine-195 of rat trypsin with cysteine in order to determine whether trypsin could be engineered to be a sulfhydryl protease.

We have surveyed protein structures for the occurrence of hydrogen bonds involving sulfur atoms. The results of this survey underscore the necessity to separate reduced cysteine from disulfide bonded half-cystine in analyzing the three-dimensional coordinates in the protein database. Cysteine behaves differently when it is reduced and when it is part of a disulfide bond. This difference is in part attributable to the differences in hydrogen bonding ability of these two types of cysteines.

## METHODS

We examined the atomic coordinates of 85 protein structures from the Brookhaven Protein Data

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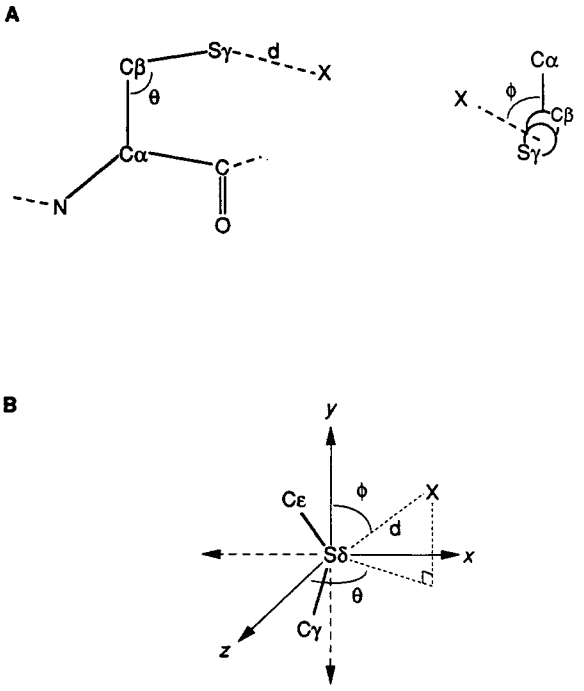


Fig. 1. **(A)** For cysteine, the location of the hydrogen bond acceptor atom (or donor atom in the case of half-cystine), X, is determined by three parameters: *d:* the distance from the γ-sulfur (Sγ) to the donor/acceptor (X), θ: the angle between the β-carbon of cysteine (Cβ), Sγ and X, and ϕ: the dihedral angle defined by the α-carbon (Cα), Cβ, Sγ, and X. **(B)** For methionine, a coordinate system is oriented with respect to the δ-sulfur (Sδ), and the ε and γ carbons (Cε, Cγ). Sδ is placed at the origin and Cε and Cγ are placed in the *y–z* plane. The bisector of the angle ∠CγSδCε is placed on the *z*-axis. The three parameters defining the position of the donor atom are *d:* the distance from Sδ to X, θ: the angle when X is projected onto the *x–z* plane, and ϕ: the angle between the *y*-axis, Sδ and X.

Bank.[10,11]* This group was selected from structures which were distinct and for which complete atomic detail is available at an experimental X-ray diffraction resolution better than or equal to 2.0 Å. All amino acids containing covalently bonded sulfur atoms (other than half-cystine) and sulfur atoms participating in metal ion binding were not evaluated. Our data set thus consisted of 109 cysteines, 307 methionines, and 268 half cystines.

All atoms within 4.25 Å of each methionine and cysteine sulfur atom were located. This distance was chosen to be long enough to include donor–acceptor pairs within van der Waals contact of each other, yet short enough to supply meaningful data. For all nearby atoms, excluding those likely to contribute to nonspecific interactions (atoms from the cysteine or methionine in question, the backbone carbonyl carbon and oxygen atoms of the preceding residue, and the backbone nitrogen of the following residue) we calculated the angles and distances defined in Figure 1. We then sorted these nearby atoms by atom type or functional group into four categories: carbon, nitrogen, carbonyl oxygen (both backbone and side chain), and hydroxyl oxygen, and prepared distributions of angles and distances for each atom or group. In order to compare the distributions, each was normalized by the number of occurrences of that particular atom or group in the data set and by the number of cysteines, methionines, or half-cystines. The distance distributions were also normalized by shell volume.

Carbon atoms do not participate in hydrogen bonding, yet short distances between nonadjacent carbon and sulfur atoms are observed in the data set of structures. X-Ray crystallographic refinement permits some small number of short contacts since the process is a least-squares minimization. Some of these short contacts are real and others are erroneous. The carbon to sulfur distance and angle distributions observed should define background levels for random interactions. In order to look for peculiarities in the distance and angle distributions for

*Data set of Brookhaven Protein Data Bank structures analyzed: 1ACX, 1ALC, 1BP2, 1CAC, 1CCR, 1CRN, 1CSE, 1ECA, 1FX1, 1GCR, 1GD1, 1GOX, 1GP1, 1HDS, 1HIP, 1HMQ, 1HNE, 1HOE, 1LZ1, 1LZT, 1MB5, 1NXB, 1PAZ, 1PCY, 1PSG, 1RDG, 1RNS, 1SGT, 1SN3, 1TON, 1UBQ, 1UTG, 2ACT, 2ALP, 2APP, 2APR, 2AZA, 2CAB, 2CCY, 2CDV, 2C12, 2CNA, 2CPP, 2CPV, 2CYP, 2FB4, 2LH1, 2LHB, 2LZM, 2MHB, 2MHR, 2OVO, 2PAB, 2PRK, 2RHE, 2RSP, 2SGA, 2SNS, 2SOD, 2WRP, 3BCL, 3C2C, 3DFR, 3EST, 3FAB, 3GRS, 3INS, 3RNT, 3RP2, 3SGB, 3TLN, 451C, 4FD1, 4FXN, 4HHB, 4PTP, 4RXN, 5CHA, 5CPA, 5CYT, 5PTI, 5TNC, 6LDH, 7RSA, 9PAP.

Fig. 2. Distance difference distributions for methionine. **(A)** Carbonyl oxygen to methionine–Sδ distances, **(B)** nitrogen to methionine–Sδ distances, and **(C)** hydroxyl oxygen to methionine–Sδ distances. The number of instances found *(N)* of each type of interaction is shown in the top right-hand corner. These distributions were prepared in the following manner: For each distance d where $d$ = 2.8, 2.9, . . . ,4.2 Å, the donor/acceptor density per residue, $\rho(d)$ is given by

$$\rho(d) = \left( \frac{n_{x \to s}(d)}{N_x} - \frac{n_{c \to s}(d)}{N_c} \right) \frac{N_{tot}}{N_{met} \cdot V_{shell}(d)}$$

and

$$V_{shell}(d) = \frac{4\pi[(d + 0.05)^3 - (d - 0.05)^3]}{3}$$

where $n_{x \to s}(d)$ is the number of atoms or functional groups of type X (e.g., –OH, carbonyl oxygen, . . .) near sulfur at a distance $d \pm 0.05$ Å

$n_{c \to s}(d)$ is the number of carbon atoms near sulfur at a distance $d \pm 0.05$ Å

$N_x$ is the total number of atoms of type X in the data set

$N_c$ is the total number of carbons

$N_{tot}$ is the total number of atoms in the data set

$N_{met}$ is the total number of methionines

The density, $\rho(d)$, therefore, may be interpreted as the excess or deficit in nitrogen bond partners at a particular distance as compared to the carbon atom density. The factor of $N_{tot}$ is an arbitrary scaling factor which scales the donors/acceptors or carbon atoms to be equal to the total number of atoms in the data set. $N_{met}$ normalizes the density to be per methionine. $V_{shell}(d)$ normalizes the density to the local shell volume.

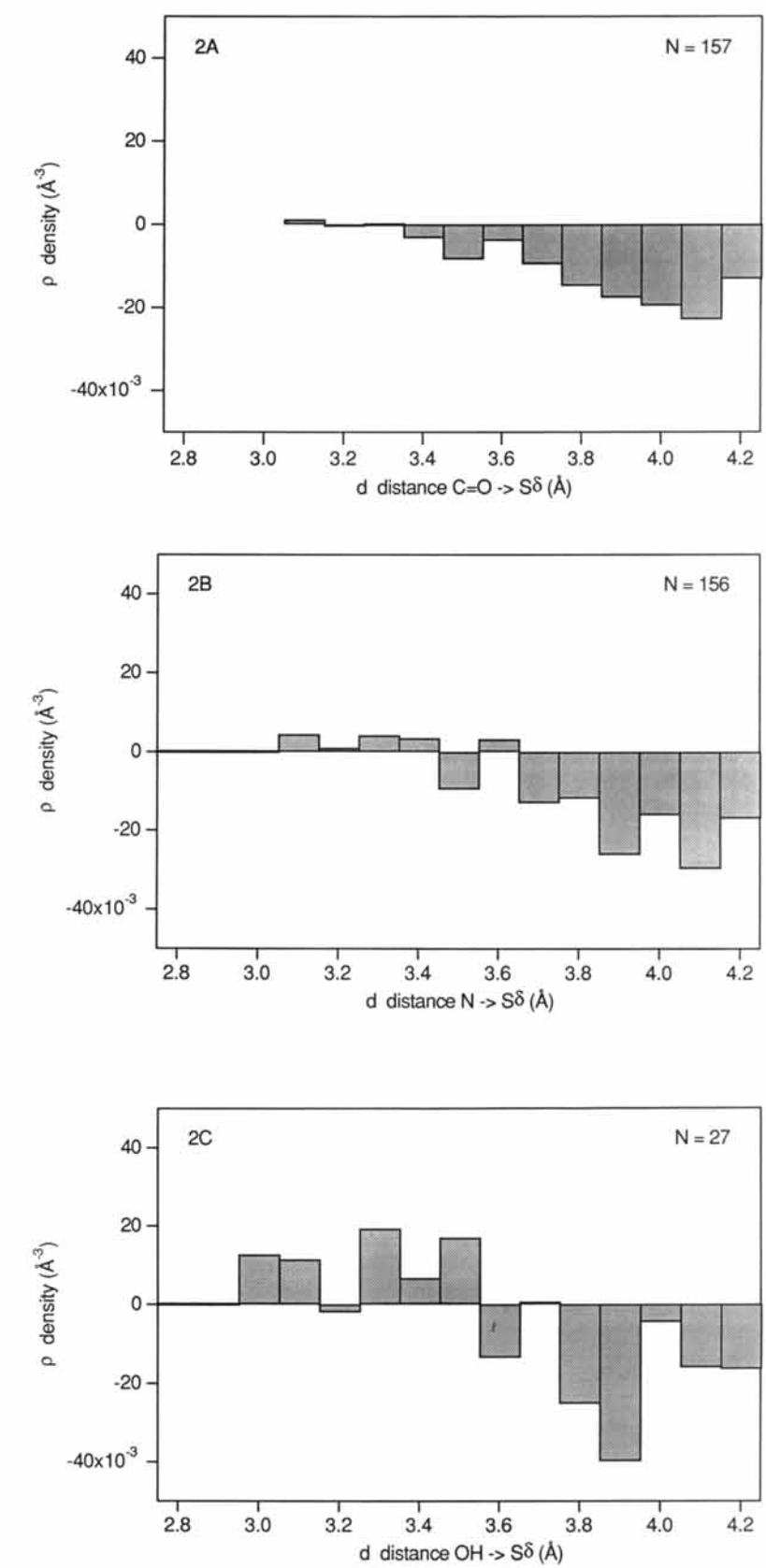
2A
N = 157
ρ density (Å-3)
40
20
0
-20
-40x10-3
2.8
3.0
3.2
3.4
3.6
3.8
4.0
4.2
d distance C=O -> Sδ (Å)
2B
N = 156
ρ density (Å-3)
d distance N -> Sδ (Å)
2C
N = 27
ρ density (Å-3)
d distance OH -> Sδ (Å)

Fig. 2.

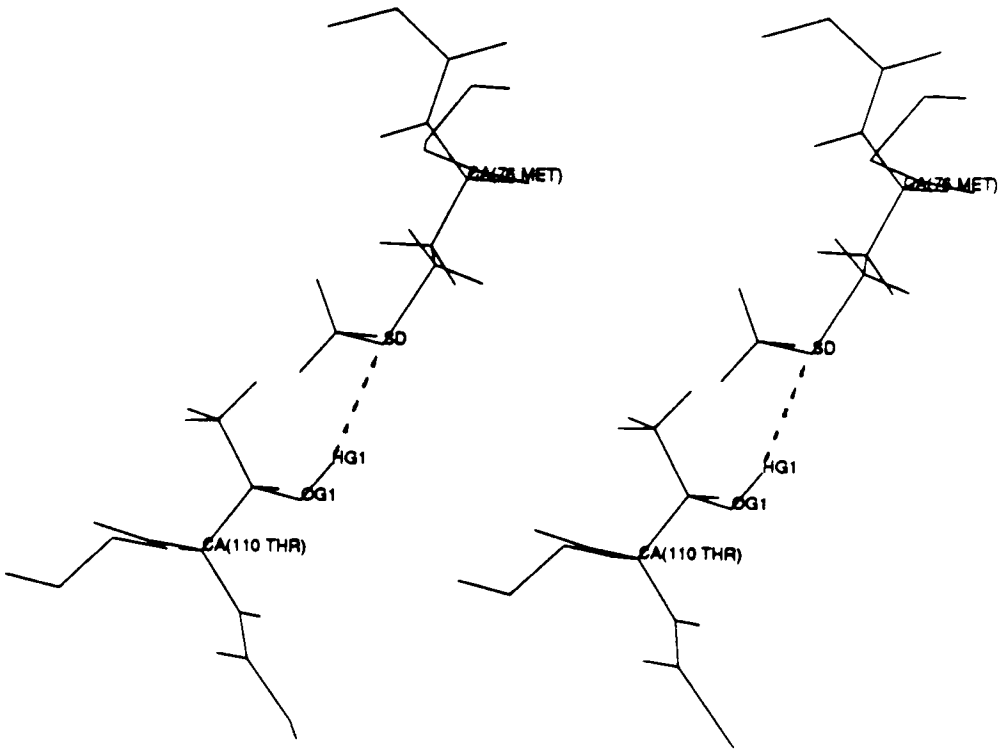


Fig. 3. Example of a hydrogen bond between the hydroxyl group of Thr-110 and Sδ of Met-76 in myohemerythrin (2MHR).[12] The Sδ to Hγ1 distance shown is 2.58 Å.

**TABLE I. Frequency of Vicinity (≤ 4.0 Å) of Potential Hydrogen Bond Donor/Acceptor Groups and Carbon***

| Potential donor or acceptor group(s) | Methionine Sδ | | Half-cystine Sγ | | Cysteine Sγ | |
|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % |
| –OH | 14 | 5 | 29 | 11 | 13 | 12 |
| $-NH_n$ | 71 | 23 | 64 | 24 | 39 | 36 |
| >C=O | 70 | 23 | 158 | 59 | 67 | 62 |
| –OH or $-NH_n$ | 78 | 25 | 85 | 32 | 47 | 43 |
| –OH, $-NH_n$ or >C=O | 118 | 38 | 177 | 66 | 78 | 72 |
| –C– | 241 | 78 | 200 | 75 | 80 | 73 |

*This table shows the frequency with which one finds potential hydrogen bond donor or acceptor groups and carbon (–OH = hydroxyl; $-NH_n$ = nitrogen; >C=O = carbonyl oxygen; –C– = carbon) in the vicinity of the sulfur atoms of methionine, half-cystine, and cysteine. *n* is the number of methionine, half-cystine, or cysteine residues with a sulfur atom within 4.0 Å of at least one member of the donor/acceptor group. % is the percentage of residues found near the donor/acceptor group. Thus, 29 of the half-cystines in the data set (or 11%) are near at least one hydroxyl group. The data set contains 307 methionines, 268 half-cystines, and 109 cysteines. When more than one group is listed as the donor/acceptor (e.g., "–OH or $-NH_n$") then the number and percentage shown are the number of sulfurs near *either* one donor/acceptor group or the other.

actual hydrogen bond donor ($-NH_n$, –OH) and acceptor (carbonyl O) groups, for each group we prepared a "difference distribution" by subtracting the normalized carbon distance or angle distribution from the distribution in question.

## RESULTS AND DISCUSSION

### Methionine

Hydrogen bonding is not particularly prevalent among methionine residues. In fact, as shown by the mostly negative distance difference distribution in Figure 2B, there are *fewer* nitrogen atoms near methionine Sδs, on average, than there are carbon atoms. This situation undoubtedly arises both because methionine is hydrophobic and thus surrounded mostly by carbon atoms, and because Sδ is usually more than 5 Å from the backbone. Nitrogen can donate hydrogen bonds while carbonyl oxygen is a hydrogen bond acceptor like Sδ of methionine. However, the distance difference distribution for car-

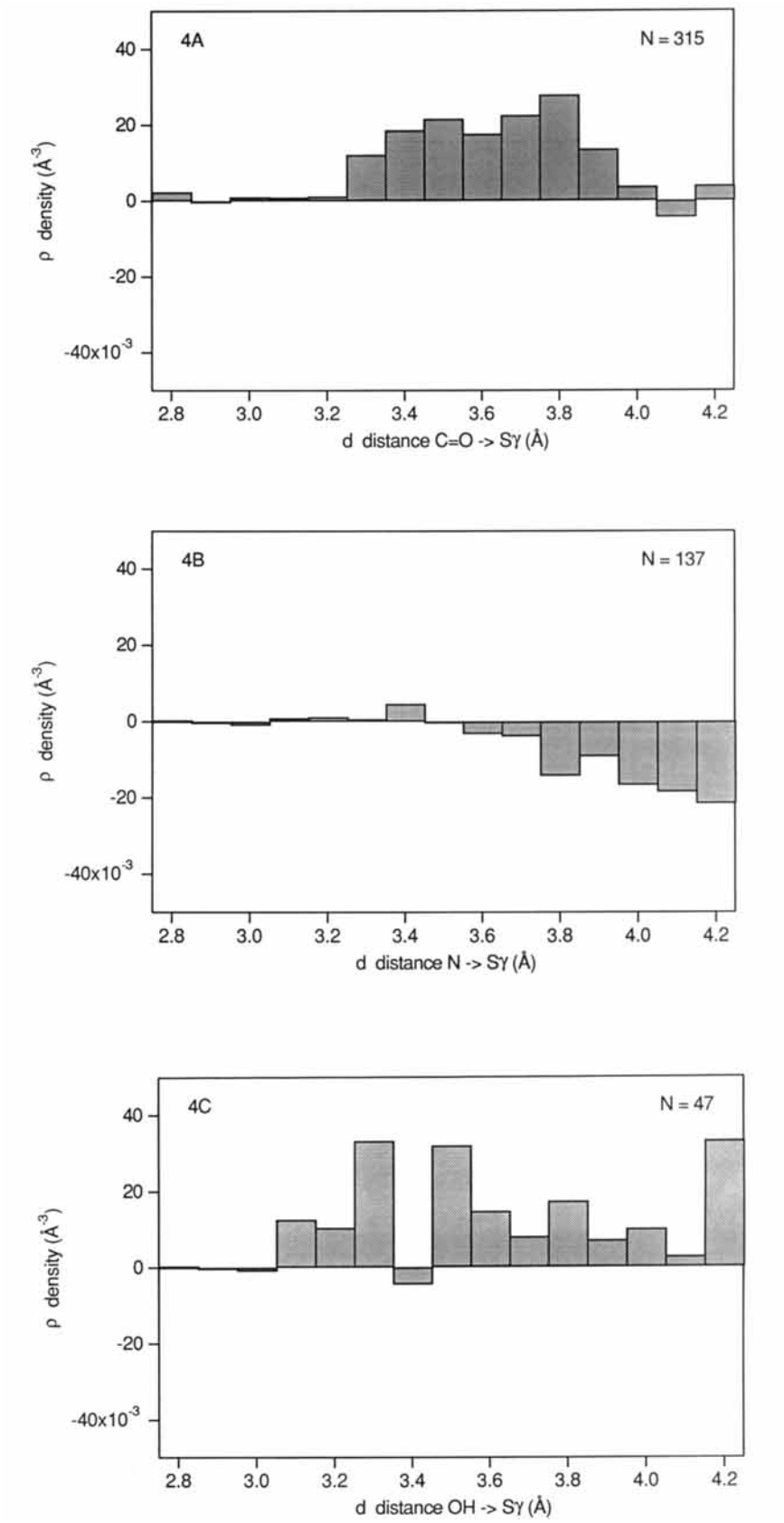


Fig. 4. Distance difference distributions for half-cystine. Histograms were prepared as described in Figure 2. **(A)** Carbonyl oxygen to half-cystine–Sγ, **(B)** nitrogen to half-cystine–Sγ, **(C)** hydroxyl oxygen to half-cystine–Sγ. The number of instances found *(N)* of each type of interaction is shown in the top right-hand corner.

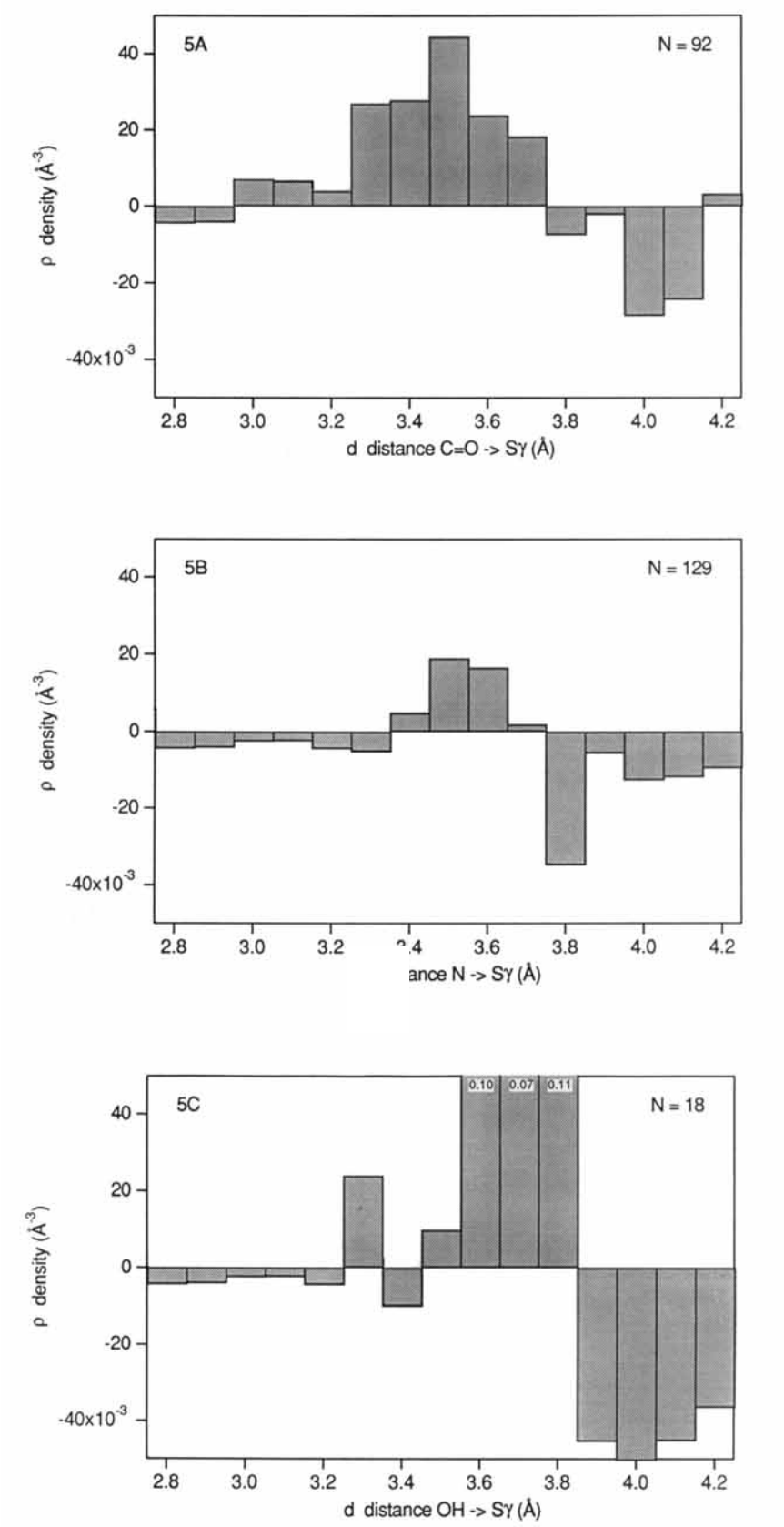


*Fig. 5. Distance difference distributions for cysteine. Histograms were prepared as in Figure 2.* **(A)** *Carbonyl oxygen to cysteine–Sγ,* **(B)** *nitrogen to cysteine–Sγ,* **(C)** *hydroxyl oxygen to cysteine–Sγ. The number of instances found (N) of each type of interaction is shown in the top right-hand corner.*

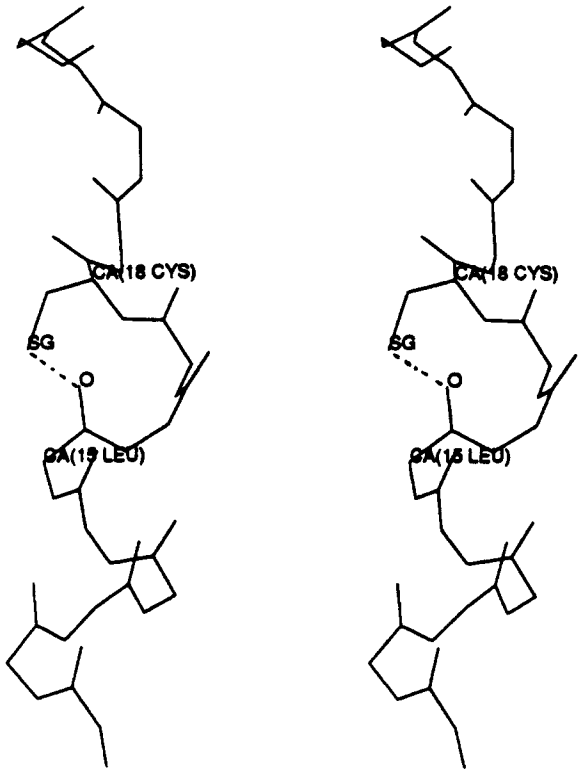


Fig. 6. Example from carp parvalbumin (1CPV)[20] of "helix capping." The unsatisfied carbonyl oxygen of Leu-15 at the C-terminal of a helix accepts a hydrogen bond from the sulfhydryl group of Cys-18. The carbonyl oxygen to Sγ distance is 3.07 Å.

bonyl oxygen is very similar to the nitrogen distribution (Fig. 2A) even though one would expect to find more short distances to nitrogen.

Close approaches between hydroxyl groups of serine, threonine, and tyrosine occur with greater frequency than close contacts to carbon, particularly in the expected hydrogen-bonding range of 3.0 to 3.6 Å (Fig. 2C). Beyond 3.6 Å, however, the frequency of carbon interactions is higher. This result suggests that methionine–Sδ—HO– hydrogen bonds are not negatively biased by X-ray crystallographic refinement schemes since few are found even in the range of van der Waals contact distance where they would be if refinement did not allow for closer contacts. We did not find any angular preferences for methionine–Sδ—HO– hydrogen bonds.

An upper limit on the frequency with which methionine participates in hydrogen bonding may be estimated by computing the number of methionine Sδs which are within 4.0 Å of either a hydroxyl group or a nitrogen. Of the methionine Sδs in our data set, 25% were within 4.0 Å of a hydroxyl oxygen or nitrogen (see Table I).

A good example of a hydrogen bond to methionine can be found in the combined neutron and X-ray structure of myohemerythrin (2MHR)[12] between the hydroxyl group of Thr-110 and the sulfur of Met-76 (Fig. 3). The Sδ–H$\gamma_1$ distance is 2.58 Å and the Sδ–O$\gamma_1$ distance is 3.50 Å. The bond is nearly linear with $\angle O\gamma_1$ H$\gamma_1$ Sδ = 163°. The donor group is not directed at either lone pair of sulfur. Rather, it is in the plane of atoms Cγ, Sδ, and Cε closer to Cγ($\theta \approx 180$; $\phi \approx 50$ for both O$\gamma_1$ and H$\gamma_1$).

### Half-Cystine

As with methionine, short distances between hydroxyl groups and γ-sulfurs of half-cystine residues are observed, suggesting that half-cystine can act as a hydrogen bond acceptor of hydroxyl (Fig. 4C). Short distances to nitrogen are rarer (Fig. 4B). Thirty-two percent of half-cystines in our data set had their Sγ within 4.0 Å of a hydroxyl oxygen or nitrogen atom (see Table I). This sets an upper limit for how frequently half-cystine participates in hydrogen bonding in proteins.

Curiously, although hydrogen bonds can not exist between carbonyl oxygen and half-cystine sulfur, we found a significant number of short distances between these groups, in the 3.3 to 4.0 Å range, with a peak at 3.8 Å (Fig. 4A). Sixteen percent (40 of 302) of carbonyl-O—Sγ short distances were between the *i*th half-cystine sulfur and the backbone carbonyl oxygen of either the $i - 2$ or the $i - 3$ residue. Upon examining these interactions further using computer graphics,[13,14] we noted that many of them occur when the $i - 2$ or $i - 3$ residue at the end of an α-helix or a β-strand and the *i*th half-cystine residue is in a turn or loop. This result is not surprising if one considers that half-cystine is most commonly observed in coil-type secondary structure and that the polypeptide chain must undergo a 180° chain reversal in order for the topological requirement of the disulfide bond to be satisfied.[15] Apart from the general observation regarding secondary structure, we could not find any other conformational similarity among the examples encountered. No angular preferences were observed among the half-cystine Sγ—donor/acceptor pairs.

### Cysteine

Of the three residue types surveyed here, cysteine participates in hydrogen bonding most frequently. Hydrogen bonds between the sulfhydryl group of cysteine and carbonyl oxygen are particularly numerous (Fig. 5A). Short distances between –SH and nitrogen (–$NH_n$) are common as well and several hydrogen bonds to between –SH and –OH were also observed (Fig. 5B,C). In all, 72% of cysteines in our data set of protein structures were found to be within less than 4.0 Å of a carbonyl oxygen, nitrogen or hydroxyl oxygen (see Table I). This gives an estimate of the frequency with which cysteine could participate in hydrogen bond formation. Most cysteines (62%) were found near carbonyl oxygens. Propor-

tionately more cysteine sulfurs were found in the vicinity of nitrogen than half-cystine or methionine sulfurs (36 vs. 23 and 24%) suggesting that cystine Sγ also has a greater propensity to behave as a hydrogen bond acceptor. This is also demonstrated in the positive distance distribution for nitrogen at 3.4–3.7 Å (Fig. 5B). We did not find any angular preferences for cysteine-Sγ—donor/acceptor pairs.

Twenty-seven contacts were found between sulfhydryl of cysteine residue $i$ and the carbonyl oxygen of residue $i - 4$. Like serine and threonine,[3] if the two residues are in a helical conformation, the sulfhydryl group of cysteine can hydrogen bond to the carbonyl oxygen of the $i - 4$ residue if cysteine adopts a $\chi_1$ angle of $-60°$. The $i - 4$th carbonyl oxygen is still able to bond to the $i$th nitrogen and helical geometry does not appear to be compromised. It has been observed that cysteine preferentially adopts a helical conformation—47% of cysteines are found in helices.[15] In glycogen phosphorylase,[16,17] 5 of 8 cysteines are in helical conformations and all of these exhibit the $i \rightarrow i - 4$ hydrogen bonding described here.

Cysteine residues just beyond the C-termini of helices can also "cap" terminal helical residues three or four residues prior in sequence by forming hydrogen bonds to their carbonyl oxygens. In this manner, the hydrogen bond requirement of one of the terminal residues is fulfilled even though the amide nitrogen of the $i + 4$th residue is not available for hydrogen bond formation. Richardson and Richardson[18] have observed greater frequencies of occurrence of serine, threonine, and glutamine near the C-termini of helices. These residues are capable of forming side chain–main chain hydrogen bonds. Presta and Rose[19] have postulated that capping residues are important for helix boundary formation during folding. An example of helix capping may be found in carp parvalbumin (1CPV)[20] between the sulfhydryl of residue number 18 and the carbonyl oxygen of leucine 15 (Fig. 6).

## CONCLUSIONS

Of the three sulfur-containing amino acids, cysteine participates in hydrogen bonding most frequently. Cysteine is found in the vicinity of hydrogen bond donating or accepting groups 72 percent of the time, most often near carbonyl oxygens. Intrahelical hydrogen bonds between the sulfhydryl group of cysteine and the carbonyl oxygen of the $i - 4$th residue are common, as is C-terminal capping, where the sulfhydryl group of cysteine donates a hydrogen to an unsatisfied carbonyl near the end of the helix. Half-cystine is also frequently found near carbonyl oxygens, though the prevalence of this interaction must be fortuitous and may have more to do with disulfide bond geometry and half-cystine's preference for coil conformation,[15] since half-cystine cannot hydrogen bond to another hydrogen bond acceptor. It is possible that hydrogen bonding ability may influence such factors as side chain conformation and secondary structural preference: intrahelical hydrogen bonding may contribute to cysteine's preference for helical conformation. Surveys of amino acid behavior in proteins should treat free cysteine and half-cystine as unique amino acids.

Sulfur behaves as a hydrogen bond acceptor less frequently. Occasional hydrogen bonds between hydroxyl groups and sulfur are observed in all three amino acid types surveyed (methionine, half-cystine, cysteine.) Hydrogen bonds between the sulfhydryl of cysteine and nitrogen are occasionally observed.

With regard to crystallographic refinement schemes, there does not appear to be a significant bias against short distances between sulfur and potential hydrogen bond donating or accepting groups. If this were the case, we would have observed a cluster of hydrogen bonds at a distance greater than the ideal hydrogen bonding distance. The peak in the distance difference distribution for cysteine–SH—O-carbonyl is where one would expect it to be—at 3.5Å as expected.

While hydrogen bonds to sulfur are not a common feature in globular proteins, their existence should be noted in protein structure modeling schemes and site-directed mutagenesis experiments.

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