Precise Molecular Structures of Cysteine, Cystine, Hydrogen-Bonded Dicysteine, Cysteine Dipeptide, Glutathione and Acetyl Cysteine Based on Additivity of Atomic Radii

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Abstract

Structures of molecules are usually represented by arbitrary line drawings, ball and stick or space filling models. In recent years, the author found that on using the appropriate radii of atoms and ions, bond lengths in inorganic, organic and biomolecules and of hydrogen bonds are exact sums of the radii of the adjacent atoms and or ions. This additivity of atomic radii was shown to hold also for the bond lengths in the twenty essential amino acids. On this basis, the atomic structures of the very important molecules mentioned in the title, have been presented here for the first time. These precise structures and their dimensions are hoped to shed new light into their role in biochemistry, pharmaceutical chemistry, environmental chemistry, biomedicine and in the mechanism of protein folding.

Keywords: Amino acids; disulfide bond; SHS hydrogen bond; NC peptide bond; Protein folding; Atomic structures

1. Introduction

Cysteine (RSH), an amino acid with a thiol (SH) group attached to an amino-carboxyl group R, and its oxidized form, cystine (RSSR) with a disulfide bond are present in intra and extra cellular components of our organisms. They are found in animal and plant proteins and in our bodies from our hair on the head to the nails in our toes. For a general introduction to these compounds along with pertinent literature, see[1,2]. Both have their characteristic properties as sulfur containing components of smaller and larger peptides and proteins. Their numerous functions and uses can be found e.g., in[2]. In environmental chemistry and toxicology, cysteine and glutathione (GSH), an important tripeptide of glutamic acid, cysteine and glycine, are good scavengers of toxic compounds and heavy metal ions as the latter can bind to the thiol sulfur. Glutathione is also a powerful antioxidant and for an account, see[3]. There is a vast and growing amount of literature on the uses and functions of cysteine and its compounds. To mention a recent one that has made headlines, N-acteyl cysteine, generally used in cough medicines[2], has found to slow down ageing[4], and might become the 'elixir of youth'. Cysteine also plays a key role in protein folding by forming a disulfide bond with another cysteine on the same or another peptide chain[5,6], see Fig. 3 in[5]. The disulfide bonds also play a key role in the structure and properties of gluten in wheat proteins[7]. A dynamic picture of protein folding by the formation of the disulfide bridge can be seen in the animation in[8].

Therefore, presented here are the exact structures at the atomic level of cysteine and the cysteine-based compounds to improve our understanding of their role and feasibility of chemical, biochemical and biomedical processes for their many uses and applications.

2. Results and discussion

Pauling[9] suggested the additivity of atomic covalent radii in covalent bonds. However, he did not use this idea to the full to establish the structures of molecules. It was shown[10] in recent years that on using the *appropriate* atomic covalent radii[9], it is possible to account for the experimental bond lengths in all molecules including the various components DNA[11] and all the amino acids[12] as sums of the radii of the adjacent atoms. In this paper, the structures of the molecules mentioned in the title are presented below in separate sections. In each case the bond lengths are sums of the appropriate covalent atomic radii of the adjacent atoms in the molecules in their unionized state.

2.1. Cysteine (RSH)

Cysteine is conventionally represented by the line drawings, ball and stick or space filling models as shown in[2]. Here, the covalent radii[12] (R_{cov}) of C, N, O, S and H atoms, which account for the known bond lengths in all amino acids, are given in Fig. 1. These values were used to obtain the radii sum, given in Table 1 for all the bonds in L-cysteine shown in Fig. 2a. Table 1 also gives the corresponding bond length values from the literature[13-15], other than the supporting data provided in[12]. The numberings of the atoms in Table 1 are the same as in[13] and shown in Fig. 2b. The CSH angle in Fig. 2a is 96^0 as in[14]. Fig. 3 shows the linear graph of the bond lengths obtained as radii sum versus the bond length data from the literature[13-15].

Cysteine has three chemically reactive groups (see Fig. 2): the sulfur of the thiol group, the hydrogen of the amino group and the OH of the carboxyl group, the latter two of which are attached to the α-carbon (C_2 in Fig. 2) . The thiol group can be oxidized to form a dilsulfide bond as in cystine. The amino hydrogen and the

carboxyl OH bond of a neighboring amino acid form a peptide linkage by eliminating a water molecule[1] as shown in[12] and in dicysteine here. In the tripeptide glutathione, the three amino acids, glutamic acid, cystiene and glycine form a tripeptide, where the OH of the carboxyl group in the side chain in glutamic acid takes part rather than the OH of the carboxyl attached to the α-carbon. The amino hydrogen of cysteine can be substituted e.g., by an acetyl group as in acetyl cysteine. The structures of all these compounds have been presented here.

2.2. Cystine (RSSH)

A cystine molecule with the disulfide bond is formed by oxidizing two cysteine molecules[2c] as shown in Fig. 4a. Figs. 4b,c show the two possible structures of cystine. The data for SS bond length are included in Table 1 and Fig. 3. In protein folding, two cysteines belonging to the same or different polypeptide chains make a cross link via the thiol groups and oxidize to form a disulfide bond and form cystine as shown in[5,6] and in the dynamic picture in[8]. Fig 4b would correspond to the cross link and oxidation of L-cysteines in the same protein chain, since the peptide links formed by the L-amino hydrogen and the OH of the carboxyl group of the adjacent amino acid would preserve this L-orientation. The structure of cystine in Fig. 4c can result in other circumstances. The CSS bond angle is about 105.6 in[14]. Note from the dimensions of cystine in Figs. 4b,c, that in protein folding, two peptide cysteines have to be 12.2 Å from each other for forming the dilsulfide linkage.

2.3 Hydrogen bonded Discysteine (RSH..SHR)

If the cross link between the cysteines in two parts of the folding protein are the make/break type as in[8], it could be due to a hydrogen bond linking the sulfurs of the

two cysteines together. For the SH...S bonding, the bond length H...S is given[16] as 2.8Å and the SH..S angle as 159^0. Figs 5 a,b show the two possible dicysteines linked by hydrogen bonds. The dimensions of the two configurations are given in the figures. These hydrogen bonded states could be the intermediate prior to the formation of the disulfide bond. An explanation of the lengths of hydrogen bonds is given in[17]. Another aspect that could influence the disulfide bonding or the SH...S bonding in protein folding is the neighborhood of cysteine in the polypeptide chain of the protein. The cross linking of the two cysteines can be either favored or disfavored in protein folding depending on whether the amino acids adjoining cysteine are oxidation friendly or not. Intracellular media favor cysteine, the reduced form and extracelllular media favor the oxidized form, cystine,[18].

2.4 Cysteine dipeptide (RSH-RSH) and the NC peptide bond

Figure 6 shows how two cysteines unite to form a dipeptide NC bond by eliminating one molecule of water. Note that sterically, the two molecules can only bond with the thiol groups in trans-position with respect to the NC peptide bond. The generally observed (1.37 Å) shorter than expected length[1,9] of the dipeptide NC bond in amino acids was explained[12] (for the first time) by the sum of the covalent double bond radius (0.67 Å) of $C_{d.b.}$ (shorter than the single bond radius, $C_{s.b.}$ = 0.77 Å, see Fig. 1) and the covalent single bond radius (0.70 Å) of $N_{s.b.}$.

2.5 A cysteine based tripeptide: glutathione (GSH)

A favorable partner which enhances the oxidizing property of cysteine especially to help scavenge toxic metal ions via binding with sulfur is the tripeptide, glutathione[3] (GSH), consisting of glutamic acid, cysteine and glycine; see[12] for the

atomic structures of the last three amino acids. GSH is a very important compound and is a powerful antioxidant. It is also found to have a vital role in the iron metabolism[19]. Fig. 7a shows the generic structures[20] and Fig. 7b, the atomic structure of glutathione.

2.6 Acetyl cysteine

Acetyl cysteine is cysteine with an amino hydrogen replaced by an acetyl group. This makes it a very important compound with many uses[21] especially as an antidote to drug overuse of medicines like paracetamol. Recently it is shown[4] to retard ageing of cells and it may become an elixir of longevity. The atomic structure of this compound along with its chemical structure is shown in Fig. 8a,b.

3. Conclusions:

This work brings for the first time the exact structures of cysteine, cystine and other cysteine compounds at the atomic level based on the additivity of *appropriate* atomic covalent radii in bond lengths. The structures of cystine with the disulfide bond, and all the other cysteine based compounds have been drawn to scale and presented here for the first time. It is hoped that this work will be of use in researches on the biochemical, biomedical and pharmacologic roles of these compounds and in the understanding of the mechanism of protein folding.

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TABLE 1: Sums of atomic radii[12] and bond lengths from the literature[13-15] for cysteine and cystine. All values in Å.

Bonds	< Radii sum >		< bond lengths >		
S1-C1	1.04+0.77=	1.81	1.82	1.80	1.84
C1-C2	0.77+0.77=	1.54	1.52	1.52	1.53
C2-C3	0.77+0.67=	1.44	1.54	1.53	1.53
C3-O1	0.67+0.70=	1.27	1.25	1.21	1.20
C3-O2	0.67+0.67=	1.34	1.27	1.33	1.36
C2-N1	0.77+0.70=	1.47	1.48	1.45	1.45
S1-S2	1.04+1.04=	2.08	2.04	2.02	-
Refs.:	12	12	13	14	15

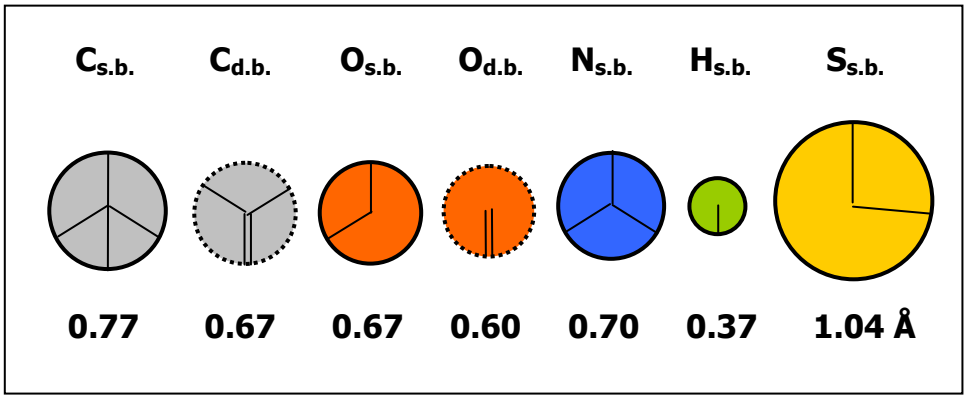


Fig. 1. The atomic covalent radii[9], R_{cov} (Å) (given under the atoms) of C (grey, tetravalent), O (orange, divalent), N (blue, trivalent), H (green, monovalent) and S (yellow, divalent) that constitute the amino acids,[12]. Subscripts s.b. and d.b. stand for single bond and double bond respectively.

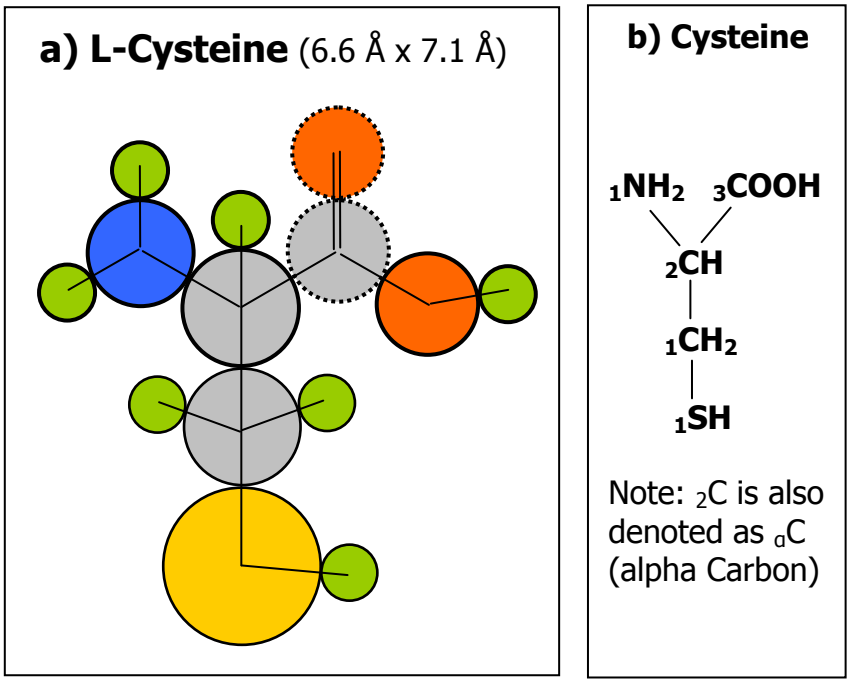


Fig. 2. Cysteine. a) Molecular structure based on additivity of covalent radii in bond lengths. b) Generic structure.

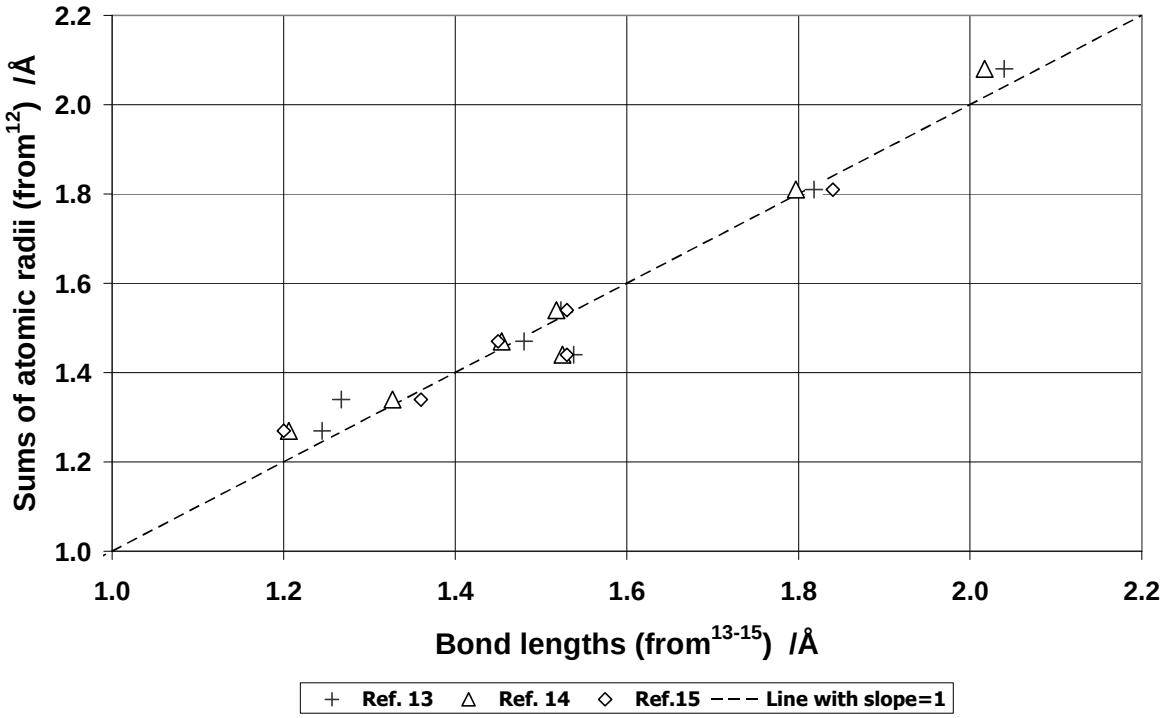


Fig. 3. Linear correlation of atomic radii sum[12] with the known bond lengths[13-15] for cysteine and cystine.

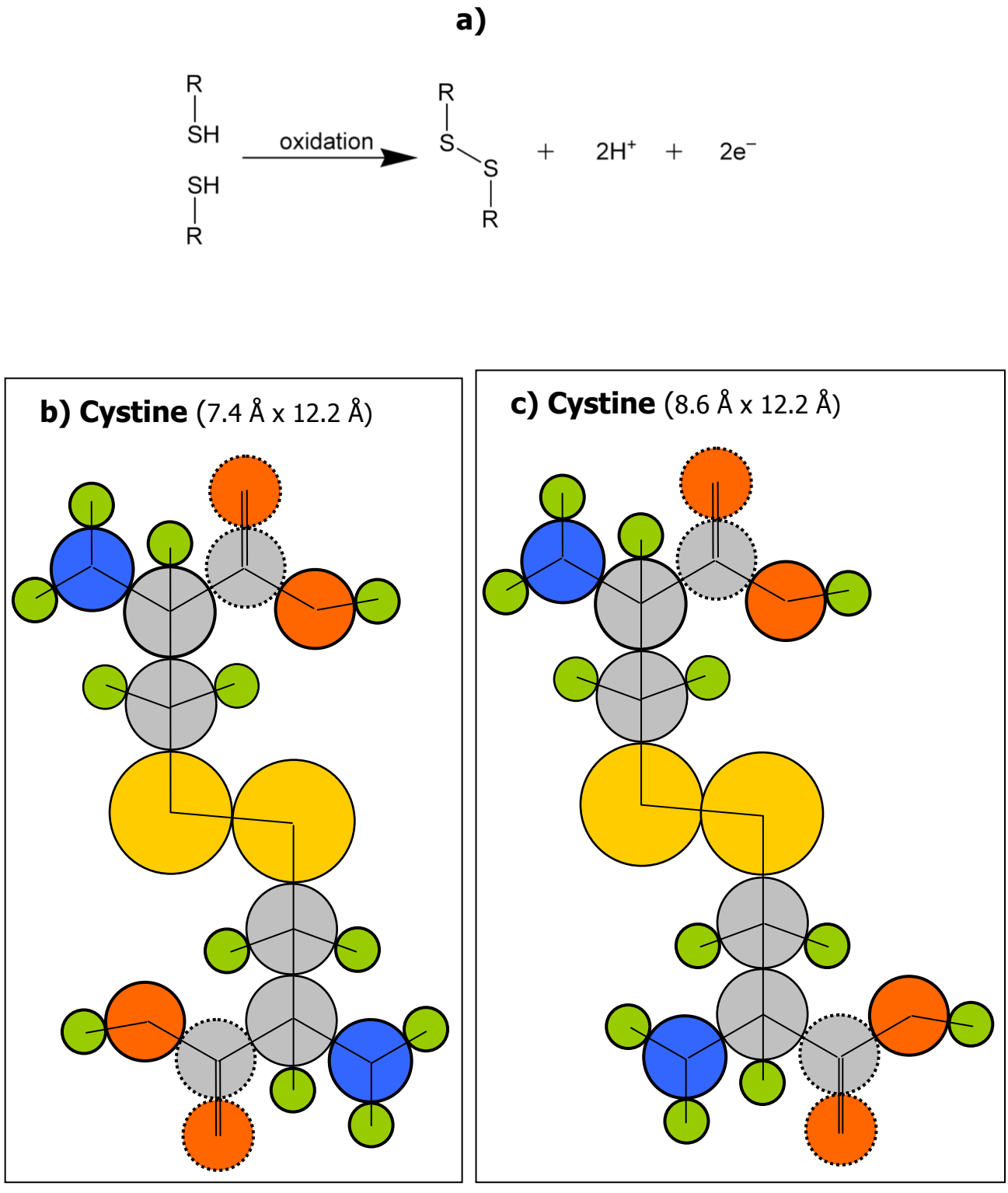
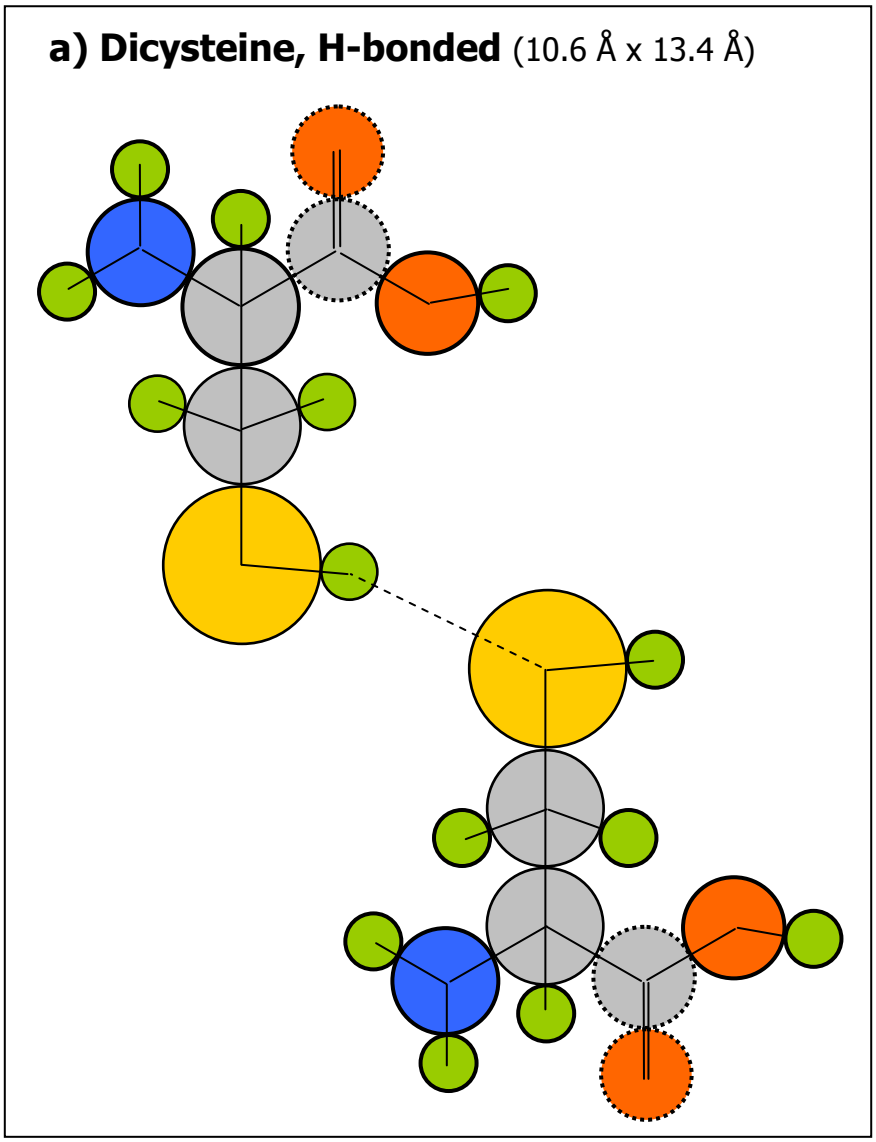


Fig. 4. Cystine. a) Oxidation of cysteine to cystine[2c], b) & c) Atomic structures of two forms based on additivity of atomic radii, with the CSS angle[14] of 96^0.

Fig. 5. a) this page and b) next page.



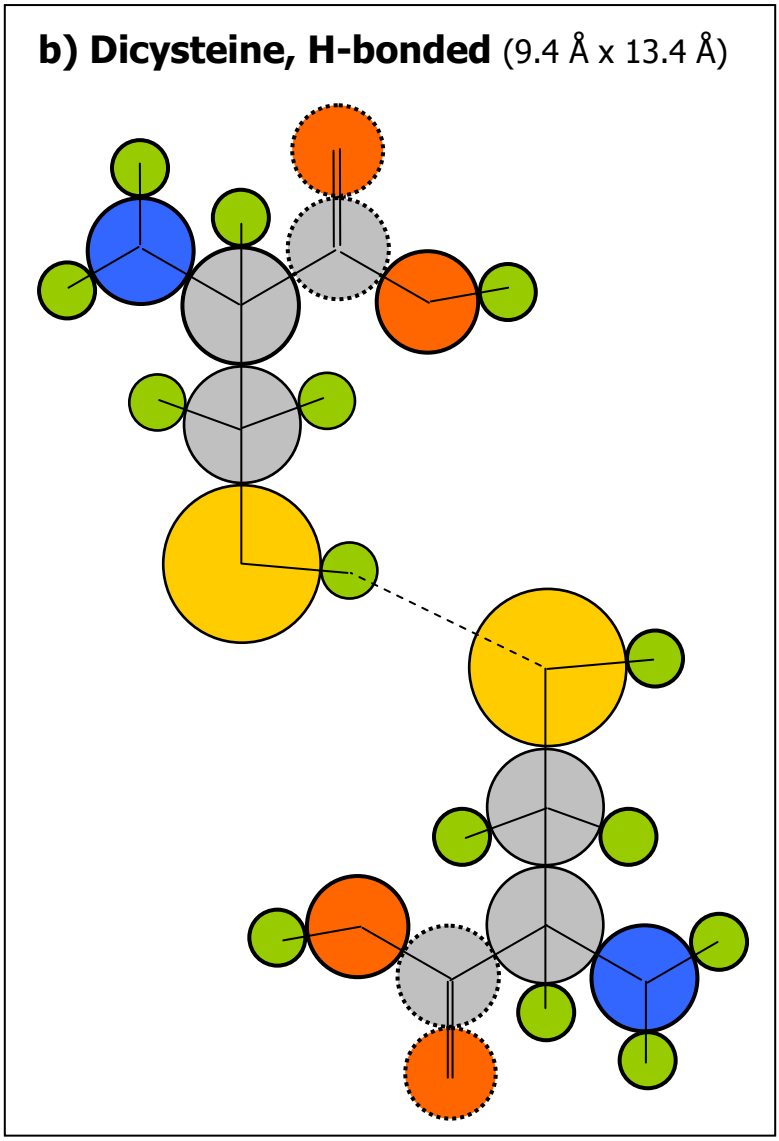


Fig 5. Dicysteine, hydrogen-bonded. a) and b) Atomic structure based on additivity of atomic radii of two hydrogen bonded forms as shown. The SH bond length = 1.41 Å,[12] S...H distance = 2.80 Å,[16] SHS angle = 159°,[16].

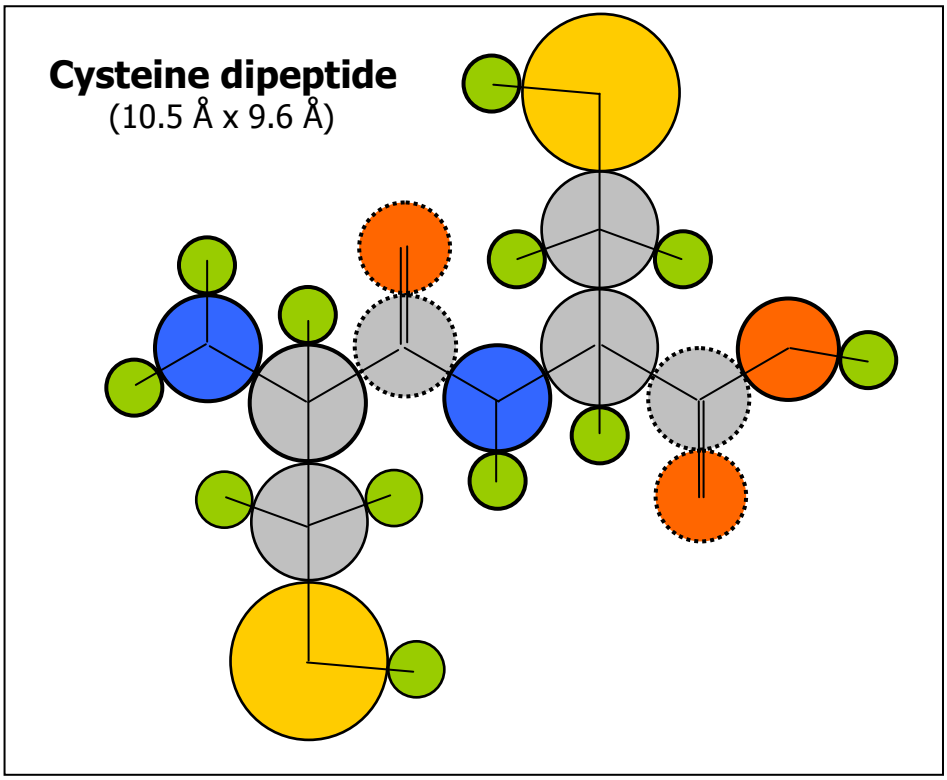


Fig 6. Cysteine dipeptide**:** Atomic structure based on additivity of atomic radii.

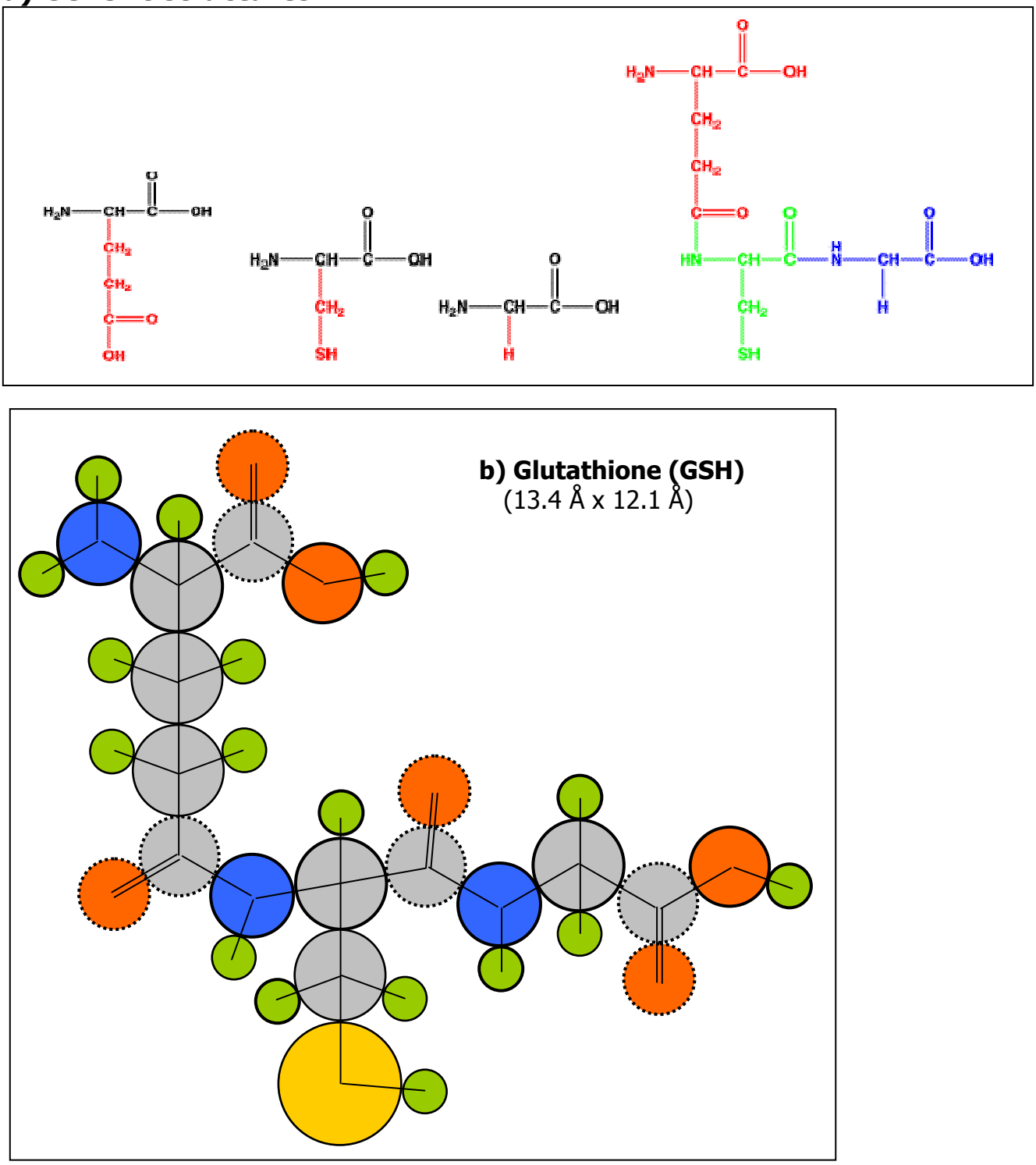


Fig. 7. Glutathione. a) Generic structures[20] of (left to right) glutamic acid, cysteine, glycine and glutathione (reproduced with permission from Niedrehofer[20]) and b) atomic structure of glutathione based on additivity of atomic radii.

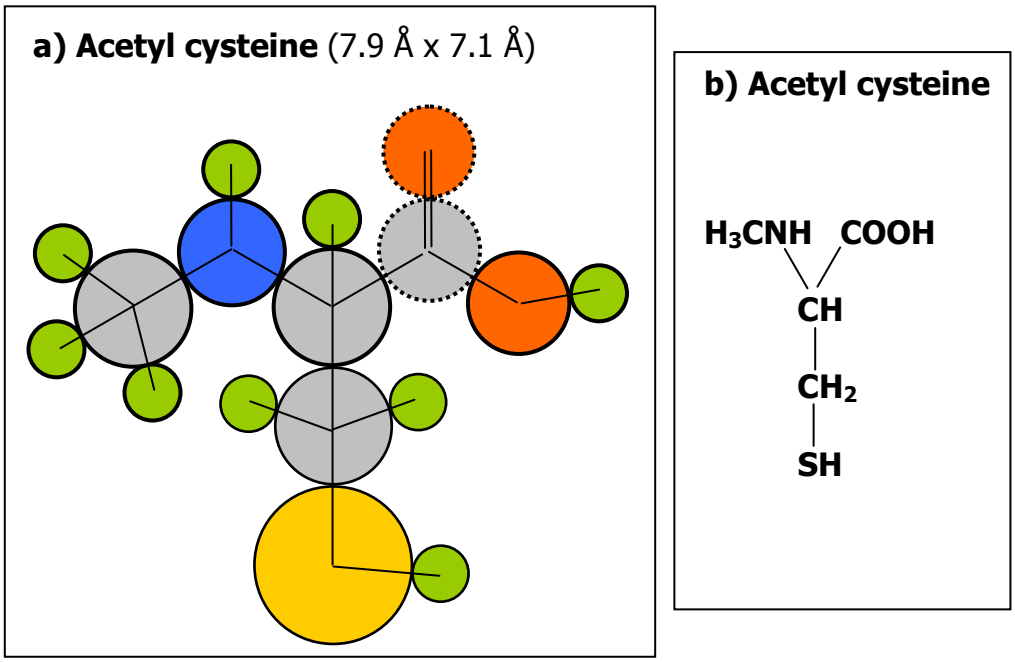


Fig 8. Acetyl cysteine. a) Atomic structure based on additivity of atomic radii. b) Generic structure.