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INTERRELATIONS BETWEEN THE ENTHALPIES OF FORMATION OF THE SULFUR-CONTAINING AMINO ACIDS L-CYSTINE, L-CYSTEINE AND L-METHIONINE

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ABSTRACT

L-Cystine, L-cysteine, and L-methionine are among the twenty-two L-α-amino acids from which all proteins are composed. With their unique sulphur atoms, L-cystine, L-cysteine, and L-methionine have been particularly problematic with regard to both qualitative and quantitative understanding of their energetics, most notably their enthalpies of formation. Using thermochemical quantities from calorimetric experiments (enthalpies of combustion, hydrogenolysis, vaporization, and sublimation), high level quantum chemical calculations, and idealized chemical reactions, these enthalpies of formation are derived and interrelated. In a brief epilogue, the conceptual trichotomy of "convenience, anthropocentrism, and folksonomy" is employed to enhance our thermochemical understanding of these species.

KEYWORDS: L-cystine, L-cysteine and L-methionine; enthalpies of formation, reaction, vaporization and sublimation; disulfides; quantum chemical calculations; sulphur-containing amino acids; trichotomy

1. Introduction

Alpha-amino acids and the derived polypeptides and proteins are essential for living organisms, e.g., all enzymes, structural biomaterials (e.g., collagen, elastin, keratin), general health (glutathione, HDL vs. LDL cholesterol, insulin, thyroxine), oxygen and electron metabolism (haemoglobin, the diverse cytochromes), and vitamins (folic acid). Accordingly, knowledge of their energetics is an indispensable part of the fundamental understanding of life. In turn, to understand proteins implies it is desirable to know the energetics of their component α-amino acids. The values of their enthalpies of formation are an essential part of this knowledge. One of the current authors (SP) recently reviewed this topic [1], wherein results from experimental calorimetric measurements and both quantum chemical and group additivity calculations were presented.

Particularly interesting and problematic amino acids include the disulfide L-cystine, along with its reduced (thiol) counterpart, L-cysteine, for which the reported enthalpy of formation values in the solid state are numerous and disparate, and the gas phase data are problematic. We opt to discuss only the values suggested in [2], because they explicitly interweave contemporary experimental practice and high-level theory.

2. Discussion

Unlike most other studies of the energetics of amino acids [1], and likewise of many other highly functionalized organic compounds, calorimetric and computational results here are simultaneously given for both the condensed phase (solid) and gas phase species. L-cystine and L-cysteine are abbreviated in this paper as Cys-S-S-Cys and Cys-SH, respectively, to emphasize the sulphur atoms, as opposed to CYT and CYS, without any stereochemistry expressed from [2], their enthalpies of formation are:

$\Delta_f H_m^o$ (Cys-S-S-Cys, s) = -1045 ± 2 kJ mol^{-1}
$\Delta_f H_m$ (Cys-S-S-Cys, g) = -761 ± 10 kJ mol^{-1}

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$\Delta_f H_m^o$ (Cys-SH, s) = -529 ± 1 kJ mol^{-1}
$\Delta_f H_m$ (Cys-SH, g) = -383 ± 2 kJ mol^{-1}

All of these quantities, except that of gaseous L-cystine, are from direct experimental measurements. The value $\Delta_f H_m^o$ (Cys-S-S-Cys, g) = -761 kJ·mol^{-1} was obtained using Gaussian-3 theory, at the G3(MP2)//B3LYP and/or G3 levels.

In the current paper, we will revisit the enthalpies of formation of L-cystine and L-cysteine, and thereby also that of the remaining sulphur-containing amino acid, L-methionine.

For our first approach, we will consider not only the enthalpies of formation of either L-cystine or L-cysteine per se, but rather the biochemically relevant hydrogenolysis/redox reaction that interrelates them. This hydrogenolysis redox reaction is most simply written as:

$$\text{Cys-S-S-Cys} + H_2 \rightarrow 2\ \text{Cys-SH} \qquad (1)$$

From the above experimental values for the solid phase species [2], the enthalpy for this reaction is -13 ± 3 kJ mol^{-1}. We start our analysis by discussing the energetics of the hydrogenolysis reactions of general disulfides as found in the gas phase.

$$\text{RS-SR} + H_2 \rightarrow 2\text{RSH} \qquad (2)$$

We consider the hydrocarbon-based R groups: CH_3^-, $C_2H_5^-$, $(CH_3)_2CH^-$, $(CH_3)_3C^-$, and $C_6H_5^-$. All the relevant thermochemical data in Table 1 are taken from the monograph of Pedley [3].

Table 1. *Enthalpy of gas phase reaction (2) with attached groups R (in kJ mol^{-1})*

R	$\Delta_f H_m$ (RSH, g)	$\Delta_f H_m$ (RS-SR, g)	ΔH_{rkn2}
CH_3^-	-23 ± 1	-25 ± 1	-21 ± 2
$C_2H_5^-$	-46 ± 1	-75 ± 1	-17 ± 2
$(CH_3)_2CH^-$	-76 ± 1		
$(CH_3)_3C^-$	-110 ± 1	-201 ± 2	-19 ± 2
$C_6H_5^-$	111 ± 1	244 ± 4	-22 ± 4

Group additivity calculations (throughout this paper, taking input values from [4]) result in an estimated value of -18 kJ mol^{-1} for reaction (2) when the sulphur atoms are bound to a sp^3 carbon atom. Almost the same value (-19 kJ mol^{-1}) is predicted when a benzenoid carbon is involved, although group contributions differ considerably. From our newly derived disulfide and thiol enthalpy of formation interrelation, the enthalpy of formation of gaseous L-cystine equals -746 ± 5 kJ mol^{-1}. Equivalently, within the associated uncertainties, the enthalpies of formation and reaction, for cysteine and cystine are consistent with those of other pairs of thiols and disulfides. These highly functionalized amino acids of interest are "normal", despite the presence of numerous functional groups and numerous conformers in both species.

Let us now ask about the energetics of the earlier reaction (2) as applied to condensed phase species. The results are shown in Table 2.

Table 2. *$\Delta_f H_m^o$ (lq) of alkyl participants in reaction (2) as found in related thiols and disulfides and the derived reaction enthalpy ΔH_{rkn2} (in kJ mol^{-1})*

R	$\Delta_f H_m^o$ (RSH, lq)	$\Delta_f H_m^o$ (RS- SR, lq)	ΔH_{rkn2}
CH_3^-	-47 ± 1	-63 ± 1	-31 ± 2
$C_2H_5^-$	-74 ± 1	-120 ± 1	-28 ± 2
$(CH_3)_2CH^-$	-106 ± 1		
$CH_3CH_2CH_2^-$	-100 ± 1	-172 ± 1	-28 ± 2
$(CH_3)_3C^-$	-141 ± 1	-255 ± 2	-27 ± 2
$CH_3(CH_2)_3^-$	-125 ±1	-223 ± 2	-27 ± 2
$(CH_3)_2CHCH_2^-$	-132 ± 1	-233 ± 1	-33 ± 2

It is seen that this liquid-phase reaction has the nearly constant enthalpy of -29 ± 3 kJ mol^{-1}, compared to -13 ± 3 kJ mol^{-1} for the solid-phase cystine-cysteine.

What, then, about the thermochemistry of the solids? We may ask about "special" interactions found in L-cystine compared to that of other amino acids. Most amino acids have one positive nitrogenous group and one negative carboxylate group. Accordingly, in the condensed phase of amino acids, there are strong electrostatic interactions, as documented by the lack of volatility of these species.

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L-cystine, an amino acid with two positive nitrogenous groups and two negative carboxylate groups, is plausibly anticipated to be involatile and, given its composition and structure, it is also likely to be thermally labile. Indeed, its fusion process at 260.5 °C (the melting point) has been shown to be irreversible [5].

How does the "special" charge distribution in L-cystine affect the enthalpy of formation for the solid species? Is the enthalpy of sublimation enhanced because it has more charges than the other amino acids, in particular L-cysteine? Or has the enthalpy of sublimation reduced because the large dipole moment of L-cysteine has plausibly been effectively replaced by a quadrupole composed of the two positive and two negative charges arising from the two "fragments"? Or is the enthalpy of sublimation a meaningless quantity because the compound decomposes upon melting, and a fortiori boiling, so it corresponds to an irreversible process? There is yet another answer: in cystine, there is no electrostatic effect of the charges of one cysteine on the other, such that all intermolecular electrostatic interactions are the sum of the two cysteine fragments. Indeed, since the -S-S- dihedral angle is approximately 90o, all quadrupole interactions deriving from the two (NH_3^+ ••• COO^-) dipoles essentially vanish, and the electrostatic contribution to the interaction of L-cystine with other molecules as manifested by the sublimation enthalpy, is twice that of two L-cysteines.

A quick investigation of the literature [3] shows, from a thermochemical perspective, that cystine and diphenyl disulfide are alone among the disulfides, and cysteine for the thiols, that are solids at STP. It is to be noted that the enthalpy of sublimation of L-cystine has been suggested to be almost the same as twice the enthalpy of sublimation of L-cysteine [2]. Relatedly, from a surprisingly simple and successful estimation approach for enthalpies of vaporization [6, 7], the desired quantity for a general disulfide, RS-SR, is very nearly twice that of the corresponding thiol, RSH. That this relation also holds for R = -$CH_2CH(NH_3^+)COO^-$ in the solid phase (and R = -$CH_2CH(NH_2)COOH$ in the vapor phase) suggests there is little interaction between these groups within a given cystine molecule, regardless of the phase. (We now acknowledge that in the current paper we are assuming the additivity of substituent effects on phase-change enthalpies. This is equivalent to ignoring any effects from interactions between functional groups on a given molecule in the solid phase- in contradiction to what is done in the considerably less simple, but numerically more successful, estimation approach of Chickos *et al.* [8]).

An alternative approach to the enthalpy of formation of gaseous L-cystine relates to the enthalpy of formation of L-methionine, (L-Met), in which R = -$(CH_2)_2SCH_3$. The enthalpy of formation of L-methionine reported by Roux *et al.* [9] is used in this study, together with the following relation (3), assumed valid for sulphides with innocuous groups chosen for R:

$$\Delta_f H_m(\text{L-Met, g}) - \tfrac{1}{2}\Delta_f H_m(\text{Cys-S-S-Cys, g}) = \Delta_f H_m^o(CH_3SCH_2CH_2R, g) - \tfrac{1}{2}[\Delta_f H_m^o(RCH_2S\text{-}SCH_2R, g)] \quad (3)$$

Wherein we now introduce the definition:

$$\delta_4(R) = \Delta_f H_m(CH_3SCH_2CH_2R, g) - \tfrac{1}{2}[\Delta_f H_m(RCH_2S\text{-}SCH_2R, g)] \quad (4)$$

We now ask: How constant is this difference quantity $\delta_4(R)$? The admittedly sparse available data for the general sulfides and disulfides are given in Table 3.

Table 3. *$\Delta_f H_m^o$ (g) of participants in reaction (4) and the derived enthalpy difference $\delta_6(R)$ (in kJ mol^{-1})*

R	$\Delta_f H_m$ ($CH_3SCH_2CH_2R$, g)	½{$\Delta_f H_m$ (RCH_2S-SCH_2R), g)	$\delta_4(R)$
CH_3^-	-82 ± 1	-37 ± 1	-45 ± 2
$C_2H_5^-$	-102 ± 1	-59 ± 1	-43 ± 2
$(CH_3)_2CH^-$	-122 ± 2	-80 ± 2	-42 ± 3

We find the near constancy of $\delta_4(R)$ as -43 ± 3 kJ mol^{-1}); thus, we hereby deduce that the difference between gas phase enthalpies of formation of L-methionine and ½(L-cystine), i.e., $\Delta_f H_m$(L-Met, g) – ½$\Delta_f H_m$(Cys-S-S-Cys, g), equals -43 ± 3 kJ mol^{-1}. Earlier we asserted $\Delta_f H_m$(Cys-S-S-Cys, g) = -761 ± 10 kJ·mol^{-1} and one half of this value is –380 kJ·mol^{-1}. Disparate values for the enthalpy of formation of gaseous L-methionine, $\Delta_f H_m$(L-Met, g), ranging from -413 to -442 kJ mol^{-1}, are suggested in References [1, 9-13]. We find here that the value found calculated as -380 + (-43) = -423 kJ mol^{-1} is in complete agreement with the value -420 ± 10 kJ mol^{-1} recommended by Roux *et al.* [9].

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We close with a preliminary discussion of yet another thermochemical comparison. We note that, with the exception of the cyclic L-proline, all α-amino acids found in proteins may be alternatively written as either R-CH(NH_3^+)COO^- (for solids) or R-CH(NH_2)COOH (for gases). For LL-cystine we have ½ [-$CH_2SSCH_2^-$], for L-cysteine, R = $HSCH_2^-$, and methionine, R = $CH_3SCH_2CH_2^-$. Earlier in this paper, we asked how "innocuous" the various hydrocarbon-based groups are, such as methyl, ethyl and phenyl. We now briefly ask the related question: how innocuous are -CH(NH_3^+)COO^- (for solids) and -CH(NH_2)COOH (for gases)? For the current study, we will now consider only gaseous species and discuss only -CH(NH_2)COOH, where we use the earlier suggested enthalpies of formation for the amino acid. We ask whether -CH(NH_2)COOH is "replaceable" by the isoelectronic -$CH(CH_3)C(=CH_2)CH_3$ and/or the roughly isosteric -$CH(CH_3)CH(CH_3)_2$. There being almost no thermochemical information on compounds with these latter groups, we now ask about the simpler hydrocarbon group isopropyl -$CH(CH_3)_2$ containing species. Let us accordingly introduce the definition:

$$\delta_5(R) = \Delta_f H_m([R\text{-}CH(NH_2)COOH, g) - \Delta_f H_m(R\text{-}CH(CH_3)_2, g) \quad (5)$$

and present the derived $\delta_5(R)$ values in Table 4.

Table 4. *The gas phase enthalpies of formation for the sulphur-containing amino acids, their corresponding simple hydrocarbon analogues, and the derived enthalpy difference (in kJ mol^{-1})*

R-	$\Delta_f H_m$(R-CH(NH_2)COOH, g)	$\Delta_f H_m$(R-CH(CH_3)$_2$, g)	δ_5(R)
½[-$CH_2SSCH_2^-$]	-380 ± 7	-88 ± 1	-292 ± 7
$HSCH_2^-$	-383 ± 2	-87 ± 1	-296 ± 2
$CH_3SCH_2CH_2^-$	-420 ± 10	-129 ± 3 [a]	-291 ± 10

[a] This value was obtained by asserting near thermoneutrality (as from group additivity reasoning) for the gas phase reaction (6) wherein $R^1 = CH_3SCH_2CH_2^-$ and $R^2 = CH_3^-$

$$R^1S\text{-}SR^1 + R^2S\text{-}SR^2 \rightarrow 2R^1S\text{-}SR^2 \quad (6)$$

A consensus value of -293 ± 5 kJ mol^{-1} may thus be suggested for the difference of the enthalpy of formation between a gaseous amino acid and its isopropyl hydrocarbon counterpart. Indeed, a consistent difference value is found for the simplest example, glycine and propane, wherein R = H, with enthalpies of formation of -394 ± 2 from [14-18] and -105 ± 1 from [3], respectively. The resulting difference is -289 ± 2 kJ mol^{-1}.

Given that the amino acids of interest are "normally" found in their solid phase, the reader may naturally ask about the corresponding difference quantity of Eq. 5 for solids. We are unfortunately thwarted here by the absence of the desired enthalpy of formation data for the isopropyl species in their solid phase.

3. Conclusions

We now acknowledge other, likewise high level, quantum chemical calculations [14, 15, 18] from which the enthalpy of formation of L-cysteine, but generally not of L-cystine, may be found. The values selected by us for the enthalpies of formation of the three sulphur-containing amino acids L-cystine, L-cysteine, and L-methionine follow the thermochemical interrelations found for simpler (i.e., less functionalized) organic sulphur compounds containing the same -SH and -S-S-bonds. The interrelations introduced in this article were explained by structural effects and are compatible with findings from diverse calorimetric experiments, quantum chemical calculations, as well as group additivity estimations of both enthalpies of formation and phase transition enthalpies.

It is to be noted that L-cystine is composed of two chiral L-cysteine moieties, and so L-cystine should have been named LL-cystine. There is the enantiomer, accordingly named DD-cystine, which has identical physical and chemical, but not biological, properties to the natural LL-species. However, there is also an additional diastereomer in which the chirality of the two "component" amino acids is opposite. Indeed, there is such a species, historically called "meso-cystine" (and abbreviated as m-CYT) that has been generally ignored [19-21]. How stable is it? There are no calorimetric investigations for this latter species. However, L-cystine, i.e., the above LL species, has been shown to slowly racemize in aqueous solutions of strong acids

to a mixture of the above diastereomers [19, 21]. The comparable abundance of these chiral and meso-species [19] suggests they have nearly identical Gibbs free energies, and very plausibly also nearly identical enthalpies. In other words, LL-cystine is expected to thermochemically behave like the simpler achiral disulfides that we also discuss in our analysis in this article.

4. Epilogue

We conclude our study with an epilogue devoted to trichotomies, the division of an attribute, concept, or class of objects or phenomena into three parts or categories, much as a dichotomy is the much more common word for division into two parts or categories. Some examples of trichotomies that are relevant to our study come to mind. The first relates to macromolecules of biochemical significance. We recognize proteins (polypeptides), polysaccharides (e.g., cellulose), and nucleic acids (both DNA and RNA in their multiple forms) as three such examples. Our concern in the current study is only with proteins, and indeed, such species considered alone, and thereby we ignore other classes of biomolecules such as histones, glycoproteins, and peptide nucleic acids.

The three major categories of biochemically significant dicoordinated, divalent sulphur-containing compounds are disulfides (e.g., L-cystine), thiols/mercaptans (e.g., L-cysteine), and sulphides/thioethers (e.g., L-methionine). We hereby acknowledge, and then choose to ignore, species such as the trisulfide (-S-S-S-) analogue of L-cystine, the hydropersulfide (-S-SH) analogue of L-cysteine, and the ethyl (-S-C_2H_5) analogue of methionine (quite sensibly called "ethionine"). After all, they lack the desired thermochemical data for us to proceed.

Chemical reactions may be exothermic, plausibly (or nearly) thermoneutral, or endothermic. The reaction of L-cystine and H_2 resulting in L-cysteine is exothermic for the two solid amino acids and plausibly thermoneutral for the gaseous species. Racemization of L-cysteine to form D-cysteine is thermoneutral. The homolytic S-S cleavage reaction of L-cystine to form a pair of L-cysteinyl radicals is endothermic.

It is unambiguous that many α-amino acids are convenient to study - how else do we understand that there are at least 15 calorimetric studies on glycine [1, 22] (the earliest dates to 1884)? For reasons cited in the Introduction, we recall the importance of these species for the functioning of living organisms, most assuredly for us as human beings, and so we may say their study is people-centered and anthropocentric. We also emphasize that α-amino acids have several subclasses such as "acidic" and "dicarboxylic acid" (cf. aspartic and glutamic acid), "basic" and diamines (cf. arginine, lysine, histidine), and the aforementioned "sulphur-containing" species. We hereby recall the conceptual utility and power of understanding general chemical phenomena in terms of the trichotomy: "convenience, anthropocentrism and folksonomy" [23, 24].

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