Structural Chemistry (2025) 37:41–45
https://doi.org/10.1007/s11224-025-02624-1

RESEARCH

Paradigms and paradoxes: what is the enthalpy of formation of triglycine or should we have asked "What are the enthalpies of formation of the triglycines"?

Stefan Perisanu[1] · Maja Ponikvar-Svet[2,3] · Kathleen Frances Edwards[4] · Joel Fredric Liebman[3]

Received: 8 September 2025 / Accepted: 14 September 2025 / Published online: 11 October 2025

Abstract
The current paper discusses the enthalpy of formation of triglycine. Upon asking "What is the enthalpy of formation of triglycine?", we find that there are two non-isomeric species that are generally referred to as "triglycine": glycylglycylglycine and nitrilotriacetic acid. In the current paper the enthalpies of formation of these two species termed "triglycines" are discussed and related to each other. In addition, a similar analysis is carried out for the related "diglycines".

Keywords α-amino acids · Diglycines, enthalpies of formation, fusion and of reaction · Glycine · Glycylglycylglycine · Nitrilotriacetic acid · Triglycine(s)

Introduction

In our recent paper we reported on the thermochemical study of the energetics of polyglycine, which included an examination of the energetics of glycine itself and its oligomers diglycine (glycylglycine), triglycine (glycylglycylglycine) [1]. In that study, we had to be even more careful than our usual practice of literature searching and subsequent analysis for most of our other publications. This extra diligence was mandated because our initial findings from SciFinder^n [2] showed that there are two non-isomeric species with the same name "triglycine", namely the aforementioned glycylglycylglycine and nitrilotriacetic acid, i.e. $NH_2CH_2CONHCH_2CONHCH_2COOH$ (and its zwitterion counterpart, $NH_3^+CH_2CONHCH_2CONHCH_2COO^-$) with the CASRN 556–33–2 (Fig. 1a) and $N(CH_2COOH)_3$ (and its zwitterion counterpart, $NH^+(CH_2COOH)_2CH_2COO^-$) with the CASRN 139–13–9 (Fig. 1b). Acknowledging that our thermochemical interest was only for the former substance, this word-related ambiguity is reminiscent of the content and intent of our recent series of articles [3, 4] wherein we interrelated the phonetic similarity of (sounds like) names of all of the elements to the trivial names of general chemical substances that are unrelated to that element. Acknowledging that we are always more interested in chemical energetics than etymology, the name of the substance of phonetic interest was accompanied by some quantity of thermochemical relevance for any chemical entity chosen.

In the current study we interrelate the enthalpies of formation of the identically named species "triglycine". Both species are solid multifunctional C, H, N, O-containing compounds that "look" something like the α-amino acid glycine itself, NH_2CH_2COOH (and implicitly also its zwitterion counterpart, $NH_3^+CH_2COO^-$). From the empirical formulae of these two triglycine species, $C_6H_{11}N_3O_4$ and $C_6H_9NO_6$ respectively, it is evident that these two species

✉ Maja Ponikvar-Svet
maja.ponikvar-svet@ijs.si

Stefan Perisanu
stefan.perisanu@upb.ro

Kathleen Frances Edwards
kathleen.edwards@faculty.umgc.edu

Joel Fredric Liebman
jliebman@umbc.edu

[1] Department of General Chemistry, National Polytechnic University of Science and Technology, 1-7 Polizu Str., 011061 Bucharest, Romania

[2] Department of Inorganic Chemistry and Technology, Jožef Stefan Institute, Jamova Cesta 39, 1000 Ljubljana, Slovenia

[3] Department of Chemistry and Biochemistry, University of Maryland, Baltimore County (UMBC), 1000 Hilltop Circle, Baltimore, MD 21250, USA

[4] Doctor of Business Administration Program, School of Business, University of Maryland Global Campus (UMGC), Largo, MD 20774, USA

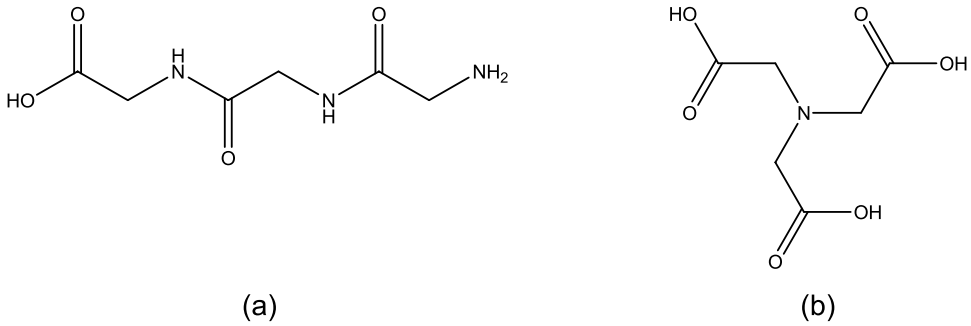

Fig. 1 Structure of (**a**) glycylglycylglycine (CASRN 556–33–2); **b** nitrilotriacetic acid (CASRN 139–13–9)

are not isomers. The first name suggests correctly that this species is a polypeptide (or more properly, the tripeptide) that is formed by the condensation of three glycine molecules. The second triglycine description suggests correctly that triglycine is the tertiary amine counterpart of glycine with its primary amino group. At this point, we wish to note that SciFinder^n [2] does not distinguish between the "neutral/nonpolar" and "zwitterionic" forms of triglycine, nor between glycine and other amino acids and their derivatives. So, why should we explicitly discuss zwitterions at all?

We ask how many of the authors of studies on either of these triglycine species (*ca*. 2500 papers and patents for glycylglycylglycine, and *ca*. 17,000 papers and patents for nitrilotriacetic acid) found in SciFinder^n [2] would agree to always use the alternative names nitrilotriacetic acid and glycylglycylglycine instead of triglycine to eliminate the ambiguity? We suspect that very few would do so. We likewise acknowledge that the use of the abbreviations "glyglygly" and "NTA" eliminates the name ambiguity but, again, we suspect that few authors would agree to this.

In view of our interest in the word-related ambiguity of chemical compounds, we must note at this point that the name "nitrilotriacetic acid" invites another nomenclature-derived problem. "Nitrile" is often used for species with C≡N triple bonds. As such, the names of compounds such as acetonitrile, CH_3CN, only further confound the ambiguity. Additionally, the name "glycine" sounds like "glycerine", now often referred to as glycerol, which we recognize as the 3-carbon compound 1,2,3-propanetriol, which correspondingly lacks nitrogen.

It is also worth mentioning that there are several other species that may also plausibly be named "triglycine". These compounds include $NH_2CH_2CON(CH_2COOH)_2$ (*N*-glycyliminodiacetic acid) and $(NH_2CH_2CO)_2NCH_2COOH$ (*N*,*N*-diglycylglycine), and their zwitterionic counterparts. However, these two additional species have been almost totally ignored by the chemical community. According to SciFinder^n [2], these compounds have received minimal attention having under ten citations *in toto*. As these references do not discuss chemical energetics, we will not explore these additional species further in this text.

Thermochemistry of nitrilotriacetic acid and glycylglycylglycine

Returning to thermochemistry, we now explicitly discuss the consistency of the reported values for the enthalpy of formation of the two substances of interest, nitrilotriacetic acid and glycylglycylglycine. As enthalpy of sublimation data is absent for both species in the experimental literature, as it is for zwitterions in general, all compounds of interest in the current study are implicitly assumed to be in their solid state.

In the absence of recent measurements of the enthalpy of formation of glycylglycylglycine, we use the value of −966 (±10) kJ mol^{-1} suggested by [5] as part of their experimental calorimetric study on hexaglycine. For nitrilotriacetic acid, we will use a value for its enthalpy of formation of –1312 (±1) kJ mol^{-1} from [6].

To make a comparison of the energetics of glycylglycylglycine and nitrilotriacetic acid, we have chosen to use a hypothetical balanced reaction in which one triglycine is a reactant and the other triglycine is a product. We thus consider the hypothetical solid phase reaction (1):

$$N(CH_2COOH)_3 + 2RCONH_2 \rightarrow NH_2CH_2CONHCH_2CONHCH_2COOH + 2RCOOH \quad (1)$$

Now, let us ask what R group is to be employed for our understanding? Since both triglycines are aliphatic species, we limit our attention only to species wherein R is likewise aliphatic. To our surprise, the only examples of R we can find are −COOH, $-C(O)NH_2$, $-C(O)CH_2CH(NH_2)COOH$, and R = $-C(O)(CH_2)_2CH(NH_2)COOH$, i.e., oxamic acid (and oxalic acid), oxalamide (and oxamic acid), asparagine (and aspartic acid), glutamine (and glutamic acid). These new species have additional hydrogen bonding and electrostatic interactions in the condensed phase that plausibly do not cancel in the reaction. We therefore conclude that none of these species are appropriate to employ in reaction (1).

It may thus appear that reaction (1) is without use as there are no appropriate choices of R to be found. We have therefore decided to relax some of the demands on the group R to be chosen. Recall that we required all of

the reagents and products to be solids. If we had chosen the simple $R = CH_3$, acetic acid, there would have been problems. This species is "naturally" a liquid, in contradistinction to all of the other species in the reaction which are appropriately solids. Let us accept this phase difference and mitigate it by the use of a consensus of the experimentally determined temperature uncorrected enthalpy of fusion values for acetic acid [7]. Accordingly with the recommended enthalpy of formation of acetamide and acetic acid from the contemporary thermochemical tables (ATcT) [8–10], let us consider the reaction (2)

$$N(CH_2COOH)_3 + 2CH_3CONH_2 \rightarrow NH_2CH_2CONHCH_2CONHCH_2COOH + 2CH_3COOH \quad (2)$$

As written this reaction is found to be exothermic by 14 (± 10) kJ mol^{-1}.

We now note in reaction (1) that the reactants are recognizable as a tertiary amine and two primary amides, while the products are likewise one primary amine, and two secondary amides. The simplest example of this type of transformation is the reaction (3), where all reactants and products are solids.

$$(CH_3)_3N + 2CH_3CONH_2 \rightarrow CH_3NH_2 + 2CH_3CONHCH_3 \quad (3)$$

Accepting the enthalpy of formation of the methylamines from [11] (with the required enthalpies of fusion from [7]), of acetamide (ATcT), and N-methylacetamide from [12] leads to the enthalpy of the new reaction (3) of -3 (± 6) kJ/mol (thermoneutral).

Based on the reactions (1) and (2) with accompanying algebraic simplification, we consider the new reaction (4). This reaction is calculated to be exothermic by 12 kJ mol^{-1}, with an uncertainty of no less than 10 kJ mol^{-1}, so large mainly because of the value given for glycylglycylglycine [5]. This allows for the possibility of thermoneutrality.

$$N(CH_2COOH)_3 + CH_3NH_2 + 2CH_3CONHCH_3 \rightarrow NH_2CH_2CONHCH_2CONHCH_2COOH + (CH_3)_3N + 2CH_3COOH \quad (4)$$

We conclude that, even if the verbal ambiguity as to which "triglycine" is meant, both species are well-characterized in terms of the enthalpy of formation values found in the thermochemical literature.

Thermochemistry of diglycine

Relatedly to triglycine, we find in SciFinder^n [2] that there are also two species with the name "diglycine", iminodiacetic acid, $NH(CH_2COOH)_2$, CASRN 142–73–4 (Fig. 2a) and glycylglycine, $NH_2CH_2CONHCH_2COOH$, CASRN 556–50–3 (Fig. 2b). The former species has ca. 8000 Scifinder^n [2] reference citations and an experimentally determined enthalpy of formation of –933 (± 1) kJ mol^{-1} [13], while the latter species there are ca. 7000 citations and an experimentally determined enthalpy of formation of –748 (± 1) kJ mol^{-1}.

Analogous to the reaction (4) for the triglycines, we write the following reaction (5).

$$NH(CH_2COOH)_2 + CH_3NH_2 + CH_3CONHCH_3 \rightarrow NH_2CH_2CONHCH_2COOH + (CH_3)_2NH + CH_3COOH \quad (5)$$

This new reaction (5) is endothermic by ca. 11 kJ mol^{-1}. We admit our surprise that the reaction (4) is plausibly exothermic, but the formally related reaction (3) is unequivocally endothermic.

The question naturally arises as to why the signs for the enthalpies of reactions (3) and (4) differ? What can be said about the thermochemical data for other aliphatic tricarboxylic acids? Besides nitrilotriacetic acid there are experimentally determined enthalpies of formation of only the tricarboxylic acids *cis*- and *trans*-aconitic acid and citric acid (and its monohydrate) as of the time of our paper as opposed to dicarboxylic acids, for which there are relatedly ca. 30 examples. As such, we may ask ourselves if we know enough to be confused?

Nonetheless, let us proceed. Let us look at the two homologous series: glycine, glycylglycine, glycylglycylglycine and glycine (aminoacetic acid), iminodiacetic acid, nitrilotriacetic acid. From the linear regression analysis performed in our previous study [1], the enthalpy of formation difference of glycylglycine and glycine is –220 kJ mol^{-1}. Likewise, the corresponding difference for glycylglycylglycine and glycylglycine is the nearly identical –218 kJ mol^{-1}. We may say that there is nothing "special" regarding the energetics of glycine, glycylglycine and glycylglycylglycine. By contrast, the corresponding difference between the enthalpy of formation of glycine and iminodiacetic acid is –528

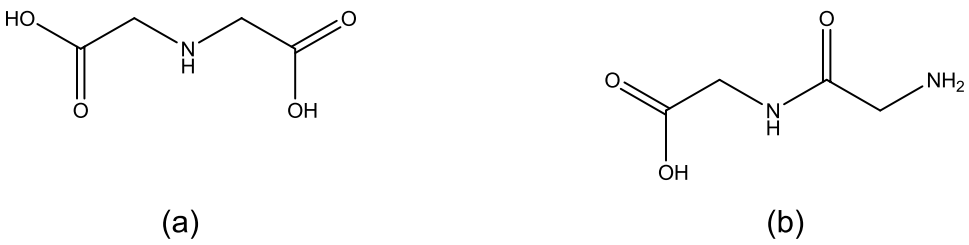

Fig. 2 Structure of (**a**) iminodiacetic acid (CASRN 142–73–4); **b** glycylglycine (CASRN 556–50–3)

–(–933) = 405 kJ mol^{-1}, while that of iminodiacetic acid and nitrilotriacetic acid is –933 –(–1312) = 379 kJ mol^{-1}. Alternatively, we may consider the enthalpy of formation difference of glycylglycine and that of ½[(glycine + glycylglycylglycine). However, the difference between iminodiacetic acid and glycine is –405 kJ mol^{-1}, while that of nitrilotriacetic acid and iminodiacetic acid is only –379 kJ mol^{-1}. From this we deduce that nitrilotriacetic acid is destabilized by (405–379) = 26 kJ mol^{-1} compared to iminodiacetic acid.

By contrast, the difference between trimethylamine/dimethylamine is –3 kJ mol^{-1} and the difference between dimethylamine/methylamine is 6 kJ mol^{-1}. Near equality of the differences in the enthalpy of formation is also seen when using enthalpy of formation data for general, but now all in their liquid, phase, trialkyl/dialkylamines and dialkyl/monoalkylamines [11, 14]. We thus conclude that nitrilotriacetic acid is significantly destabilized, while glycylglycylglycine is neither stabilized nor stabilized, a result implicitly supported by the statistical analyses found in ref. [1] for general polyglycines.

In other words, from this analysis we would conclude that nitrilotriacetic acid is expected to be more stable (or at least no less stable) relative to iminodiacetic acid than iminodiacetic acid is relative to glycine. And yet we know the opposite is found.

Discussion

Finally, let us return to our statement that nitrilotriacetic acid, iminodiacetic acid and aminoacetic acid/glycine are all zwitterions. Our earlier question was "Why should we care about zwitterions?" In what follows, we explicitly consider that these species are zwitterions, at least in the solid phase, and that concludes our discussion. In each molecule of zwitterionic nitrilotriacetic acid, we have one carboxylate anion and two carboxylic acid moieties. Likewise, in the zwitterionic iminodiacetic acid we have one carboxylate anion and one carboxylic acid moieties and in aminoacetic acid/glycine we have a solitary carboxylate anion. Let us consider unambiguous molecular situations in which we have in turn one carboxylate anion and two carboxylic acid moieties, one carboxylate anion and one carboxylic acid moieties and a solitary carboxylate anion. Assuming all zwitterion enthalpy of formation corrections are constant [15], let us thus consider $CH_3COO^-\bullet(HOOCCH_3)_2$, $CH_3COO^-\bullet HOOCCH_3$ and CH_3COO^- all as isolated anions independent of solvent and counterion alike, as mimics of nitrilotriacetic acid, iminodiacetic acid and glycine. The first is recognized as an acetate ion that is hydrogen bonded to two neutral acetic acids in an ion–molecule complex, the second as an acetate ion that is likewise solvated by a single acetic acid molecule, and the third as an unsolvated acetate ion. The total hydrogen-bonding energy for the first ion–molecule complex has been experimentally shown [16] to be 123 kJ mol^{-1} and for the second 82 kJ mol^{-1}. There is a net destabilization of 123–82 = 41 kJ mol^{-1} for our gas phase nitrilotriacetic acid mimic relative to its iminodiacetic acid mimic. compared to iminodiacetic acid and glycine. We earlier deduced that nitrilotriacetic acid is destabilized relative to iminodiacetic acid by 405–379 = 26 kJ mol^{-1}. The two values of destabilization associated with nitrilotriacetic acid and glycylglycylglycine as deduced by our two approaches discussed above are 41 and 26 kJ mol^{-1}, These two numerical values are not numerically identical. However, given that they were derived by very different assumptions and yet are numerically comparable within the large uncertainty associated with the enthalpy of formation of glycylglycylglycine (ca. 10 kJ mol^{-1}), we have hereby provided a plausible explanation for the thermochemical results for all solid aminoacids of interest in our study glycine, nitrilotriacetic acid and glycylglycylglycine, iminodiacetic glycylglycine and iminodiacetc acid. Indeed, while the words "triglycine" and "diglycine" remain ambiguous, the thermochemistry of these species is now well-understood.

Conclusion

Despite the ambiguity of the names, both the triglycine and diglycine species are well characterized in terms of the values of the enthalpy of formation. When analyzing the zwitterionic forms of these species, we observed a consistent pattern of hydrogen bonding interactions and associated energetic differences, providing a plausible explanation for the thermochemical inequality among the species studied. This highlights the importance of zwitterionic structures in influencing the stability and behavior of amino acids and related compounds, both in the solid state and in aqueous solution.

Acknowledgements We wish to thank Arthur Greenberg and the reviewers of our earlier paper [1] for helpful comments on our study.

Author contributions All authors (SP, MPS, KFE, JFL) have contributed equally to writing and reviewing the manuscript.

Funding MPS gratefully acknowledges the Slovenian Research and Innovation Agency (ARIS Grant P1-0045, Inorganic Chemistry and Technology) for financial support.

Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval We did not perform any experiments when preparing this article, and so neither ethics review nor informed consent was necessary.

Consent to participate All authors agreed with participation in research and publication of the results.

Consent to publish All authors have approved the manuscript before submission, including the names and order of authors.

Competing interest The authors declare no competing interests.

References

1. Perisanu S, Ponikvar-Svet M, Edwards KF, Liebman JF (2025) Paradigms and paradoxes: If polyglycine is the polymer, then what is the monomeric repeating unit? Struct Chem. https://doi.org/10.1007/s11224-025-02563-x
2. SciFinder^{n}. American Chemical Society, Washington, DC. Accessed July 2025
3. Ponikvar-Svet M, Edwards KF, Liebman JF (2023) Paradoxes and paradigms: elements and compounds: similar names, very different energetics. Part I, Hydrogen-to-argon (H - Ar) Z = 1–18. Struct Chem 34:1205–1217. https://doi.org/10.1007/s11224-022-02103-x
4. Ponikvar-Svet M, Edwards KF, Liebman JF (2023) Paradoxes and Paradigms: elements and compounds: Similar names, very different energetics. Part 5, Selected examples of exotic species and isotopes (H, He, C, F, U). Struct Chem 34:2365–2374. https://doi.org/10.1007/s11224-023-02208-x
5. Colbert JC, Domalski ES, Coxon B, Vanderhart DL (1989) Bomb calorimetric and NMR studies on crystalline hexaglycine. Thermochim Acta 153:123–141. https://doi.org/10.1016/0040-6031(89)85428-0
6. Vasil'ev VP, Borodin VA, Kopnyshev SB (1989) Standard heats of formation of ethylenediaminedisuccinic acid and NTA. Zh Fiz Khim 63:1343–1345
7. Acree W, Chickos JS (2016) Enthalpy measurements of organic and organometallic compounds. Sublimation, vaporization and fusion enthalpies from 1880 to 2015. Part 1. C1–C10. J Phys Chem Ref Data 45:033101. https://doi.org/10.1063/1.4948363
8. Ruscic B, Bross DH (2025) Active thermochemical tables (ATcT) values based on ver. 1.220 of the Thermochemical Network. atct.anl.gov
9. Ruscic B, Bross DH (2025) Accurate and reliable thermochemistry by data analysis of complex thermochemical networks using active thermochemical tables: the case of glycine thermochemistry. Faraday Discuss 256:345–372. https://doi.org/10.1039/D4FD00110A
10. Ruscic B, Pinzon RE, Morton ML, von Laszewski G, Bittner S, Nijsure SG, Amin KA, Minkoff M, Wagner AF (2004) Introduction to active thermochemical tables: Several "key" enthalpies of formation revisited. J Phys Chem A 108:9979–9997. https://doi.org/10.1021/jp047912y
11. Dorofeeva OV, Filimonova MA, Marochkin II (2019) Aliphatic amines: a critical analysis of the experimental enthalpies of formation by comparison with theoretical calculations. J Chem Eng Data 64:5630–5647. https://doi.org/10.1021/acs.jced.9b00680
12. Roux MV, Jiménez P, Daválos JZ, Castaño O, Molina MT, Notario R, Herreros M, Abboud JLM (1996) The first direct experimental determination of strain in neutral and protonated 2-azetidinone. J Am Chem Soc 118:12735–12737. https://doi.org/10.1021/ja962792w
13. Vasilev VP, Borodin VA, Kopnyshev SB (1988) Standard enthalpies of combustion and formation of iminodiacetic and ethylenediaminetetraacetic acids. Zh Fiz Khim 62:2243–2246
14. Steele WV, Chirico RD, Knipmeyer SE, Nguyen A, Smith NK, Tasker IR (1996) Thermodynamic properties and ideal-gas enthalpies of formation for cyclohexene, phthalan (2,5-dihydrobenzo-3,4-furan), isoxazole, octylamine, dioctylamine, trioctylamine, phenyl isocyanate, and 1,4,5,6-tetrahydropyrimidine. J Chem Eng Data 41:1269–1284. https://doi.org/10.1021/je960093t
15. Domalski ES, Hearing ED (1993) Estimation of the thermodynamic properties of carbon-hydrogen-nitrogen-oxygen-sulfur-halogen compounds at 298.15 K. J Phys Chem Ref Data 22:805–1159. https://doi.org/10.1063/1.555927
16. Meot-Ner M, Sieck LW (1986) The ionic hydrogen bond and ion solvation. 5. OH•O– Bonds. Gas-phase solvation and clustering of alkoxide and carboxylate anions. J Am Chem Soc 108:7525–7529. https://doi.org/10.1021/ja00096a047