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Conformers of dehydrogenated glycine isomers

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Abstract

We report a comprehensive ab initio investigation of the conformers of dehydrogenated glycine radicals using the STO-3G, 3-21G, and aug-cc-pVDZ (aVDZ) basis sets and the UHF and UMP2 (H_2N-CH-COOH and HN-CH_2-COOH) as well as MCSCF and MRCI (H_2N-CH_2-COO) methods via two different conformational search strategies generating initial structures for optimizations by (a) removing H atoms from glycine conformers and (b) scanning torsional angles describing internal rotation along the CC, CN, and CO (except for H_2N-CH_2-COO) bonds of the radicals. We find four H_2N-CH-COOH {In_{CH}, IIn_{CH}, $IIIn_{CH}$, IVn_{CH}} and seven HN-CH_2-COOH {Ip_{NH}, IIp_{NH}, $IIIn_{NH}$, IVp_{NH} Vn_{NH}, VIp_{NH}, $VIIp_{NH}$} conformers with classical(adiabatic) relative energies of {0.00(0.00), 1.57(1.55), 5.25(5.03), 9.85(9.72)} and {0.00(0.00), 0.78(1.06), 1.93 (2.08), 3.34(3.16), 3.39(3.29), 5.00(4.86), 9.27(8.87)} kcal/mol, respectively, obtained with UCCSD(T)-F12b/aug-cc-pVTZ(+UCCSD(T)-F12b/aVDZ ZPE correction) and four H_2N-CH_2-COO {Ip_{COO}, IIn_{COO}, $IIIp_{COO}$, IVn_{COO}} conformers with MRCI-F12+Q/aVDZ(+MRCI/aVDZ ZPE correction) energies of {0.00(0.00), 1.65(1.64), 1.78(1.75), 2.21(2.21)} kcal/mol, where n and p denote C_1 and C_s symmetry. The MRCI-F12+Q [UCCSD(T)-F12b] $In_{CH} \rightarrow Ip_{NH}$ and $In_{CH} \rightarrow Ip_{COO}$ classical(adiabatic) isomerization energies are 18.51(17.32)[21.20(20.01)] and 31.88(31.66) kcal/mol, respectively.

KEYWORDS

ab initio, amino acids, conformational search, explicitly correlated, glycine radical conformers

1 | INTRODUCTION

Reactive free radicals can damage biomolecules in the human body causing serious diseases. One of the most harmful radicals is OH, which may abstract a hydrogen atom from proteins thereby damaging their structure and functionality. Hydrogen abstraction can occur from the backbone and the amino-acid side chains of the polypeptides. The accurate theoretical description of such processes is extremely challenging, because one should deal with macromolecules in aqueous environment. The simplest model system of proteins is their smallest building block, which is the amino acid glycine, which is zwitterionic (^+H_3N-CH_2-COO^-) in solution and neutral (H_2N-CH_2-COOH) in the gas phase. The conformers and properties of gaseous glycine were thoroughly investigated by various electronic structure theories and experimental techniques during the past couple of decades.[1–12] Radicals can abstract a H atom by breaking the CH, NH, or OH bond resulting in a dehydrogenated glycine radical H_2N-CH-COOH, HN-CH_2-COOH, or H_2N-CH_2-COO, respectively. The OH + glycine reaction and the structures and energetics of the glycine radicals have been extensively investigated focusing mainly on the CH abstraction channel and the lowest energy conformer of H_2N-CH-COOH.[13–24] This may be explained by the fact that the C-terminal channels are energetically favored over NH and OH bond cleavages[13,16,18] and CH abstraction may happen in proteins, whereas the amino and carboxyl groups form peptide bonds, where OH bond does not exist and the electronic structure of the NH bond is altered. Nevertheless, a

few studies[13,16–18,21] considered the lowest energy conformer of HN-CH$_2$-COOH and others[13,18] reported several conformers of all the three isomer radicals derived from homolytic CH, NH, and OH bond dissociation. The above-mentioned theoretical studies employed density functional theory (usually B3LYP) and the MP2 method with double- and triple-zeta basis sets (usually 6-31G* and 6–311+ +G**).[13–19,21–23] The use of the more sophisticated and accurate CCSD(T) method is rare and only employed for single-point energy computations.[14,21]

In the present study, we report a comprehensive ab initio study of the conformers of gas-phase glycine radicals considering CH, NH, and OH bond dissociations. We go beyond the accuracy of the previous studies by applying the explicitly correlated CCSD(T)-F12b method[25] to obtain benchmark structures and relative energies of the dehydrogenated glycine isomers. Besides the high-level ab initio investigation of the glycine radicals, we test different computational strategies to determine all the possible conformers of the title system, which techniques may become useful for mapping the conformational space of other similar or even larger systems.

The motivation of the present study is multiple-fold: (a) We determine conformers of glycine with the state-of-the-art explicitly correlated CCSD(T)-F12b method, for the first time, thereby confirming and/or improving previous work.[1,4] (b) We aim to find new conformers for the dehydrogenated glycine radicals, thereby complementing previous incomplete studies.[13–24] (c) We provide benchmark structures and energetics for the conformers of glycine radicals. (d) As the topology of the potential energy surface may sensitively depend on the level of electronic structure theory, we test different ab initio methods, including also multi-reference techniques, and basis sets to find radical conformers. Knowing the performance of the low-level methods can provide useful guidance for the investigations of larger systems, when the use of high-level theories is not feasible. (e) The present benchmark characterization of the dehydrogenated glycine radicals may be the first step toward the study of the OH + glycine reaction.

In Section 2, we describe the computational details including the introduction of two different conformational search strategies. The results are presented and discussed in Section 3. The article ends with summary and conclusions in Section 4.

2 | COMPUTATIONAL DETAILS

2.1 | Conformers of glycine

Following the pioneering electronic structure studies reporting eight conformers (see Figure 1) of the gaseous glycine,[1,4] we optimize these conformers and compute their harmonic frequencies using the second-order Møller–Plesset perturbation theory (MP2)[26] combined with the correlation-consistent aug-cc-pVDZ basis set.[27] Then, we further optimize the obtained structures by the explicitly correlated coupled-cluster singles, doubles, and perturbative triples method (CCSD(T)-F12b)[25] using the aug-cc-pVDZ and aug-cc-pVTZ basis

sets.[27] Besides MP2, the harmonic frequencies are also computed at the CCSD(T)-F12b/aug-cc-pVDZ level of theory.

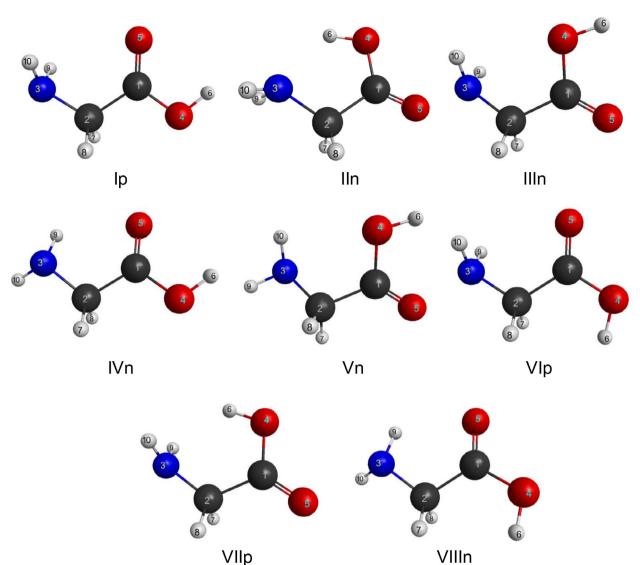### 2.2 | Conformers of dehydrogenated glycine isomers

Our goal is to determine all the possible conformers of the dehydrogenated glycine radicals. To achieve this goal we investigate two different strategies and various levels of electronic structure theory as detailed below.

2.2.1 | Strategy I

As a first, simple, chemically motivated strategy we remove one H atom from the central C atom, the amino or the carboxyl group of each of the eight glycine conformers. Since the two CH$_2$ and NH$_2$ hydrogen atoms are equivalent in the three C_s glycine geometries and different in the five C_1 structures, the H abstraction leads to 3 + 2 × 5 = 13, 3 + 2 × 5 = 13, and eight different initial radical geometries for the H$_2$N-CH-COOH, HN-CH$_2$-COOH, and H$_2$N-CH$_2$-COO isomers, respectively. In the case of H$_2$N-CH-COOH and HN-CH$_2$-COOH we perform geometry optimizations starting from the above two times 13 initial structures using the following levels of theory: UHF/STO-3G, UHF/3-21G, UHF/aug-cc-pVDZ, UMP2/STO-3G, UMP2/3-21G, and UMP2/aug-cc-pVDZ.[28–31,27] For the 8 H$_2$N-CH$_2$-COO geometries we experience convergence problems in Hartree-Fock[32] (both ROHF and UHF); thus, the use of the multi-configurational self-consistent field (MCSCF)[33] and multi-reference configuration interaction (MRCI)[34] methods is found to be necessary. Therefore, we optimize the H$_2$N-CH$_2$-COO geometries using the MCSCF/STO-3G, MCSCF/3-21G, MCSCF/aug-cc-pVDZ, MRCI/STO-3G, MRCI/3-21G, and MRCI/aug-cc-pVDZ levels of theory starting from the eight initial structures. The MCSCF computations utilize a small active space of five electrons on three spatial orbitals and we compute the ground electronic state only. During all the correlation computations in this study, the core electrons are kept frozen.

2.2.2 | Strategy II

In order to ensure that we have found all the possible conformers with Strategy I, we perform a more systematic mapping of the conformational space of the glycine radicals. Starting from the lowest-energy conformer obtained by Strategy I for each of the three isomers, we generate 6^3 = 216, 6^3 = 216, and 6^2 = 36 initial geometries by varying 3, 3, and 2 torsion angles between 0° and 360° with 60° steps (6 different angle values as 0° and 360° are equivalent). The torsional motions describe the internal rotations of the {NH$_2$, COOH, OH}, {NH, COOH, OH}, {NH$_2$, COO} groups for H$_2$N-CH-COOH, HN-CH$_2$-COOH, and H$_2$N-CH$_2$-COO, respectively, as shown in Figure 2. From the above 216, 216, and

FIGURE 1 Conformers of glycine. p and n denote C_s and C_1 point-group symmetry, respectively [Color figure can be viewed at wileyonlinelibrary.com]
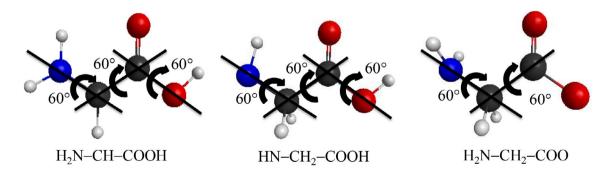

FIGURE 2 Internal rotations of the dehydrogenated glycine isomers [Color figure can be viewed at wileyonlinelibrary.com]

36 structures we initiate geometry optimizations using the ab initio methods and basis sets described in Section 2.2.1. From the unique conformers obtained by the lower levels of theory using either Strategy I or II UMP2/aug-cc-pVDZ (H_2N-CH-COOH and HN-CH_2-COOH) and MRCI/aug-cc-pVDZ (H_2N-CH_2-COO)

optimizations are initiated to assign each conformer to one of the UMP2/aug-cc-pVDZ or MRCI/aug-cc-pVDZ structures or to verify a new conformer. Note that for the MCSCF conformers obtained from Strategy II this assignment is not performed owing to the large number of conformers.

2.2.3 | Benchmark structures and energies

The final UMP2/aug-cc-pVDZ conformers obtained by Strategies I and II are further optimized using the ROHF-based UCCSD(T)-F12b[35] method with the aug-cc-pVDZ (geometry and frequency computation) and aug-cc-pVTZ (geometry) basis sets. Thus, the best classical relative energies of the H_2N-CH-COOH and HN-CH_2-COOH conformers are obtained at the UCCSD(T)-F12b/aug-cc-pVTZ level of theory and the adiabatic relative energies include UCCSD(T)-F12b/aug-cc-pVDZ zero-point energy corrections. For the H_2N-CH_2-COO conformers the classical relative energies are determined using the Davidson-corrected[36] MRCI+Q[34] and MRCI-F12+Q[37] methods with the aug-cc-pVDZ basis set at the MRCI/aug-cc-pVDZ geometries and the adiabatic relative energies are obtained utilizing MRCI/aug-cc-pVDZ zero-point energy (ZPE) corrections. In order to compare the energies of all the glycine radical isomers, MRCI+Q/aug-cc-pVDZ and MRCI-F12+Q/aug-cc-pVDZ energies are also computed for the H_2N-CH-COOH and HN-CH_2-COOH conformers at the UCCSD(T)-F12b/aug-cc-pVTZ geometries. Furthermore, MRCI/aug-cc-pVDZ frequencies are determined for the lowest-energy H_2N-CH-COOH conformer to obtain ZPE-corrected isomerization energy between H_2N-CH-COOH and H_2N-CH_2-COO. All the ab initio computations in this study are performed using the MOLPRO[38] program package.

3 | RESULTS AND DISCUSSION

3.1 | Conformers of glycine

The structures and relative energies of the eight conformers (minima) of glycine are given in Figure 1 and Table 1, respectively. The notation of the conformers follows previous studies,[1–4] that is, roman numbers increase with the energy of C_s structures and p and n refer to planar (C_s symmetry) and nonplanar (C_1 symmetry) arrangements of the N-C-COOH atoms, respectively. Three conformers (Ip, VIp, and VIIp) have C_s symmetry, whereas in five cases (IIn, IIIn, IVn, Vn, and VIIIn) lone-electron-pair repulsion effects favor symmetry breaking; thus,

the minima are nonsymmetric and the C_s structures (not shown in Figure 1) correspond to saddle points.[1] The symmetry-breaking stabilizer effects change the energy order of the III and IV conformers, that is, IVn is below IIIn by about 0.5 kcal/mol in agreement with previous studies.[1,4] For the glycine conformers the MP2/aug-cc-pVDZ level of theory provides remarkably accurate relative energies with only about 0.1 kcal/mol mean and 0.2 kcal/mol maximum differences from the CCSD(T)-F12b/aug-cc-pVDZ results as shown in Table 1. The CCSD(T)-F12b relative energies obtained with the aug-cc-pVDZ and aug-cc-pVTZ basis sets agree within 0.00–0.03 kcal/mol showing the excellent basis-convergence of the explicitly-correlated CCSD(T)-F12b method. The present CCSD(T)-F12b/aug-cc-pVTZ classical relative energies are in excellent agreement (the average absolute deviation is less than 0.1 kcal/mol) with the final predictions of Császár,[1] confirming that the "conservative" error bar estimate of ±0.3 kcal/mol given in Császár[1] was really conservative. Furthermore, the present benchmark classical relative energies reproduce the CCSD(T)/complete-basis-set(CBS) results of Balabin[4] within 0.03 kcal/mol on average, showing the superiority of the CCSD(T)-F12b method over the traditional and more time-consuming CCSD(T) CBS-extrapolation techniques. As Table 1 shows the ZPE corrections are between −0.3 and +0.4 kcal/mol with varying signs, where MP2 and CCSD(T)-F12b are in good agreement again. These ZPE corrections are clearly not negligible considering that the CCSD(T)-F12b classical relative energies are basis-set-converged within about 0.03 kcal/mol. The final adiabatic relative energies are in the same order as the classical ones, confirming the Ip, IIn, IVn, IIIn, Vn, VIp, VIIp, and VIIIn energy order of previous theoretical predictions.[1,4]

3.2 | Conformers of dehydrogenated glycine isomers

3.2.1 | Strategy I

Geometry optimizations initiated from the eight glycine conformers after removing different H atoms result in 4, 7, and 4 conformers

TABLE 1 Classical and adiabatic relative energies (kcal/mol) of glycine conformers obtained at different levels of theory[a]

	Classical			ΔZPE		Adiabatic[b]		
	MP2/ aVDZ	CCSD(T)-F12b/aVDZ	CCSD(T)-F12b/aVTZ	MP2/ aVDZ	CCSD(T)-F12b/aVDZ	MP2/ aVDZ	CCSD(T)-F12b/aVDZ	CCSD(T)-F12b/aVTZ[c]
Ip	0.00	0.00	0.00	+0.00	+0.00	0.00	0.00	0.00
IIn	0.54	0.66	0.68	+0.28	+0.35	0.82	1.01	1.03
IIIn	1.59	1.73	1.73	+0.06	+0.04	1.65	1.77	1.77
IVn	1.25	1.23	1.23	−0.01	−0.02	1.24	1.21	1.21
Vn	2.43	2.59	2.62	+0.08	+0.08	2.51	2.67	2.70
VIp	4.86	4.79	4.80	−0.15	−0.17	4.71	4.62	4.63
VIIp	6.06	5.92	5.89	−0.18	−0.10	5.88	5.82	5.79
VIIIn	6.25	6.05	6.06	−0.25	−0.14	6.00	5.91	5.92

[a]Results correspond to optimized geometries obtained by MP2/aug-cc-pVDZ, CCSD(T)-F12b/aug-cc-pVDZ, and CCSD(T)-F12b/aug-cc-pVTZ.
[b]Classical relative energy plus zero-point energy correction (ΔZPE).
[c]CCSD(T)/aug-cc-pVTZ classical relative energy plus CCSD(T)/aug-cc-pVDZ ΔZPE.
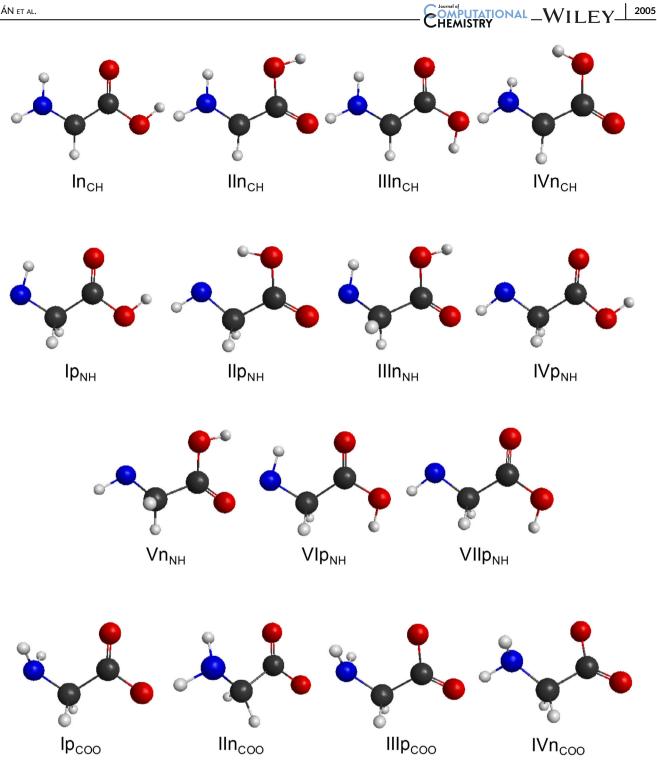
FIGURE 3 Conformers of dehydrogenated glycine isomers. p and n denote C_s and C_1 point-group symmetry, respectively [Color figure can be viewed at wileyonlinelibrary.com]

(minima) for the $H_2N\text{-}CH\text{-}COOH$, $HN\text{-}CH_2\text{-}COOH$, and $H_2N\text{-}CH_2\text{-}COO$ radicals as shown in Figure 3. Similar to glycine, the radical conformers are denoted by roman numbers reflecting the UMP2/aug-cc-pVDZ or MRCI/aug-cc-pVDZ energy order, p and n denote C_s and C_1 point-group symmetry, respectively, and subscripts CH, NH, and COO denote the radical isomer.

All the four $H_2N\text{-}CH\text{-}COOH$ conformers are nonsymmetric and related to each other by internal rotations along the CC and CO axes.

Torsional motion of the NH_2 group does not result in additional minima. Removing H atoms from glycine conformers {Ip, IIn, IIIn, IVn, Vn, VIp, VIIp, VIIIn} results in radical conformers {In_{CH}, IVn_{CH}, IIn_{CH}, In_{CH}, IIn_{CH}, $IIIn_{CH}$, IVn_{CH}, $IIIn_{CH}$} regardless which H atom is removed from the C_1 structures and which level of theory is used as shown in Table 2. The sole exemption is the case of $Vn\text{-}H_7$ (see Table 2) at the UMP2/STO-3G level, which results in In_{CH} instead of IIn_{CH}. As seen above, each radical conformer is obtained from two glycine

TABLE 2 Relative energies (kcal/mol) of $H_2N\text{-}CH\text{-}COOH$ conformers obtained from the eight glycine conformers at different levels of theory[a]

Initial structure[b]	UHF			UMP2		
	STO-3G	3-21G	aVDZ	STO-3G	3-21G	aVDZ
$Ip\text{-}H_7$	—[c]	0.70 (In_{CH})	0.09 (In_{CH})	3.13[d] (In_{CH})	0.00 (In_{CH})	0.01 (In_{CH})
$IIn\text{-}H_7$	2.97 (IVn_{CH})	—[c]	8.81 (IVn_{CH})	2.74[d] (IVn_{CH})	14.92[d] (IVn_{CH})	11.85 (IVn_{CH})
$IIn\text{-}H_8$	—[c]	—[c]	8.81 (IVn_{CH})	2.74[d] (IVn_{CH})	14.92 (IVn_{CH})	11.85 (IVn_{CH})
$IIIn\text{-}H_7$	—[c]	0.00 (IIn_{CH})	1.16 (IIn_{CH})	—[c]	0.83[d] (IIn_{CH})	2.32 (IIn_{CH})
$IIIn\text{-}H_8$	0.00 (IIn_{CH})	0.00 (IIn_{CH})	1.16 (IIn_{CH})	—[c]	0.83 (IIn_{CH})	2.32 (IIn_{CH})
$IVn\text{-}H_7$	—[c]	0.70 (In_{CH})	0.00 (In_{CH})	—[c]	0.00 (In_{CH})	0.00 (In_{CH})
$IVn\text{-}H_8$	0.35 (In_{CH})	0.70 (In_{CH})	0.00 (In_{CH})	—[c]	0.00 (In_{CH})	0.00 (In_{CH})
$Vn\text{-}H_7$	—[c]	0.00 (IIn_{CH})	1.16 (IIn_{CH})	0.73[d] (In_{CH})	0.83 (IIn_{CH})	2.33 (IIn_{CH})
$Vn\text{-}H_8$	—[c]	0.00 (IIn_{CH})	1.16 (IIn_{CH})	0.00[d] (IIn_{CH})	0.83 (IIn_{CH})	2.32 (IIn_{CH})
$VIp\text{-}H_7$	—[c]	8.39 ($IIIn_{CH}$)	6.04 ($IIIn_{CH}$)	6.47[d] ($IIIn_{CH}$)	8.88 ($IIIn_{CH}$)	5.80 ($IIIn_{CH}$)
$VIIp\text{-}H_7$	—[c]	11.99[d] (IVn_{CH})	9.64 (IVn_{CH})	5.59[d] (IVn_{CH})	14.91 (IVn_{CH})	11.85 (IVn_{CH})
$VIIIn\text{-}H_7$	—[c]	8.39 ($IIIn_{CH}$)	5.94 ($IIIn_{CH}$)	6.47[d] ($IIIn_{CH}$)	8.88 ($IIIn_{CH}$)	5.79 ($IIIn_{CH}$)
$VIIIn\text{-}H_8$	3.44 ($IIIn_{CH}$)	8.39 ($IIIn_{CH}$)	5.94 ($IIIn_{CH}$)	6.47[d] ($IIIn_{CH}$)	8.87 ($IIIn_{CH}$)	5.79 ($IIIn_{CH}$)

[a]The assignment of the conformers (see Figure 3), obtained by UMP2/aug-cc-pVDZ computations initiated from the lower-level optimized structure, are shown in parentheses.
[b]Initial structure of the geometry optimization obtained by removing the indicated H atom from the given glycine conformer (see Figure 1).
[c]UHF convergence problems or the optimization did not converge within 100 steps.
[d]Imaginary frequencies are obtained.

TABLE 3 Relative energies (kcal/mol) of $HN\text{-}CH_2\text{-}COOH$ conformers obtained from the eight glycine conformers at different levels of theory[a]

Initial structure[b]	UHF			UMP2		
	STO-3G	3-21G	aVDZ	STO-3G	3-21G	aVDZ
$Ip\text{-}H_9$	0.00 (Ip_{NH})	0.00 (Ip_{NH})	0.00 (Ip_{NH})	0.00[c] (Ip_{NH})	0.00 (Ip_{NH})	0.00 (Ip_{NH})
$IIn\text{-}H_9$	2.52 (IIp_{NH})	2.98 (IIp_{NH})	2.37 (IIp_{NH})	2.53[c] (IIp_{NH})	2.05 (IIp_{NH})	0.81 (IIp_{NH})
$IIn\text{-}H_{10}$	2.52 (IIp_{NH})	2.98 (IIp_{NH})	2.37 (IIp_{NH})	2.53 (IIp_{NH})	2.05 (IIp_{NH})	0.81 (IIp_{NH})
$IIIn\text{-}H_9$	0.64 ($IIIn_{NH}$)	2.07 ($IIIp'_{NH}$)	2.22 ($IIIn_{NH}$)	0.62[c] ($IIIn_{NH}$)	2.01 ($IIIn_{NH}$)	1.78 ($IIIn_{NH}$)
$IIIn\text{-}H_{10}$	2.26[c] ($IIIp'_{NH}$)	2.07 ($IIIp'_{NH}$)	2.22 ($IIIn_{NH}$)	0.00 (Ip_{NH})	2.01[c] ($IIIn_{NH}$)	1.78 ($IIIn_{NH}$)
$IVn\text{-}H_9$	2.06 (IVp_{NH})	4.34 (IVp_{NH})	3.18 (IVp_{NH})	2.26[c] (IVp_{NH})	4.14 (IVp_{NH})	2.98 (IVp_{NH})
$IVn\text{-}H_{10}$	0.00 (Ip_{NH})	0.00 (Ip_{NH})	0.00 (Ip_{NH})	0.00 (Ip_{NH})	0.00 (Ip_{NH})	0.00 (Ip_{NH})
$Vn\text{-}H_9$	0.64 ($IIIn_{NH}$)	2.07 ($IIIp'_{NH}$)	2.22 ($IIIn_{NH}$)	0.62[c] ($IIIn_{NH}$)	2.01 ($IIIn_{NH}$)	1.78 ($IIIn_{NH}$)
$Vn\text{-}H_{10}$	1.60 (Vn_{NH})	5.28 (Vn_{NH})	3.01 (Vn_{NH})	1.99[c] (Vn_{NH})	5.48 (Vn_{NH})	3.08 (Vn_{NH})
$VIp\text{-}H_9$	4.79 (VIp_{NH})	8.39 (VIp_{NH})	5.89 (VIp_{NH})	4.59[c] (VIp_{NH})	7.52 (VIp_{NH})	5.03 (VIp_{NH})
$VIIp\text{-}H_9$	2.52 (IIp_{NH})	2.98 (IIp_{NH})	2.37 (IIp_{NH})	2.53 (IIp_{NH})	2.05 (IIp_{NH})	0.81 (IIp_{NH})
$VIIIn\text{-}H_9$	7.98 ($VIIp_{NH}$)	8.39 (VIp_{NH})	10.14 ($VIIp_{NH}$)	4.59 (VIp_{NH})	7.52 (VIp_{NH})	9.01 ($VIIp_{NH}$)
$VIIIn\text{-}H_{10}$	4.79 (VIp_{NH})	8.39 (VIp_{NH})	5.89 (VIp_{NH})	4.59 (VIp_{NH})	7.52 (VIp_{NH})	5.03 (VIp_{NH})

[a]The assignment of the conformers (see Figure 3), obtained by UMP2/aug-cc-pVDZ computations initiated from the lower-level optimized structure, are shown in parentheses.
[b]Initial structure of the geometry optimization obtained by removing the indicated H atom from the given glycine conformer (see Figure 1).
[c]Imaginary frequencies are obtained.

conformers, which have the same COOH conformation, but different NH_2 arrangements. UMP2 with both the 3-21G and aug-cc-pVDZ basis sets gives the qualitatively same four conformers with 2–3 kcal/mol basis-set effects and with the same energy order. At the UMP2/STO-3G level the energy order changes and six different conformers

are obtained as conformers with relative energies of 0.73 and 3.13 kcal/mol are both assigned (based on further UMP2/aug-cc-pVDZ optimizations) to In_{CH} and the IVn_{CH} conformer is split to relative energies of 2.74 and 5.59 kcal/mol. Considering the structures of the above four UMP2/STO-3G conformers, the ones at 0.73, 3.13,
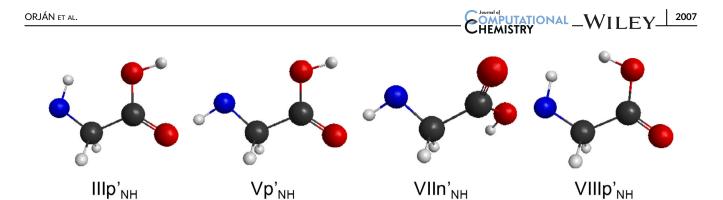
FIGURE 4 Transition-state structures of HN-CH$_2$-COOH [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 4 Relative energies (kcal/mol) of H$_2$N-CH$_2$-COO conformers obtained from the eight glycine conformers at different levels of theory[a]

Initial structure[b]	MCSCF			MRCI		
	STO-3G	3-21G	aVDZ	STO-3G	3-21G	aVDZ
Ip-H$_6$	0.00 (Ip$_{COO}$)	0.00 (Ip$_{COO}$)	0.00 (Ip$_{COO}$)	0.00 (Ip$_{COO}$)	0.00 (Ip$_{COO}$)	0.00 (Ip$_{COO}$)
IIn-H$_6$	1.41 (IVn$_{COO}$)	2.34 (IVn$_{COO}$)	2.89[c]	1.52 (IVn$_{COO}$)	2.91 (IVn$_{COO}$)	2.96[d]
IIIn-H$_6$	1.46[e] (Ip$_{COO}$)	1.69 (IIIp$_{COO}$)	1.76 (IIIp$_{COO}$)	1.19 (Ip$_{COO}$)	2.29 (IIIp$_{COO}$)	1.82 (IIIp$_{COO}$)
IVn-H$_6$	1.60 (IIn$_{COO}$)	2.66 (IIn$_{COO}$)	1.64 (IIn$_{COO}$)	1.69 (IIn$_{COO}$)	2.92 (IIn$_{COO}$)	1.64 (IIn$_{COO}$)
Vn-H$_6$	2.03 (IVn$_{COO}$)	—[f]	—[f]	—[f]	4.52[e] (IVn$_{COO}$)	2.21 (IVn$_{COO}$)
VIp-H$_6$	0.00 (Ip$_{COO}$)	0.00 (Ip$_{COO}$)	0.00 (Ip$_{COO}$)	0.00[e] (Ip$_{COO}$)	0.00 (Ip$_{COO}$)	0.00 (Ip$_{COO}$)
VIIp-H$_6$	1.98[e] (IIIp$_{COO}$)	2.46[e] (IVn$_{COO}$)	—[f]	—[f]	3.43[e] (IVn$_{COO}$)	—[f]
VIIIn-H$_6$	—[f]	0.00 (Ip$_{COO}$)	—[f]	—[f]	0.00 (Ip$_{COO}$)	1.64 (IIn$_{COO}$)

[a]The assignment of the conformers (see Figure 3), obtained by MRCI/aug-cc-pVDZ computations initiated from the lower-level optimized structure, are shown in parentheses.
[b]Initial structure of the geometry optimization obtained by removing the indicated H atom from the given glycine conformer (see Figure 1).
[c]Further MRCI/aug-cc-pVDZ optimization fails.
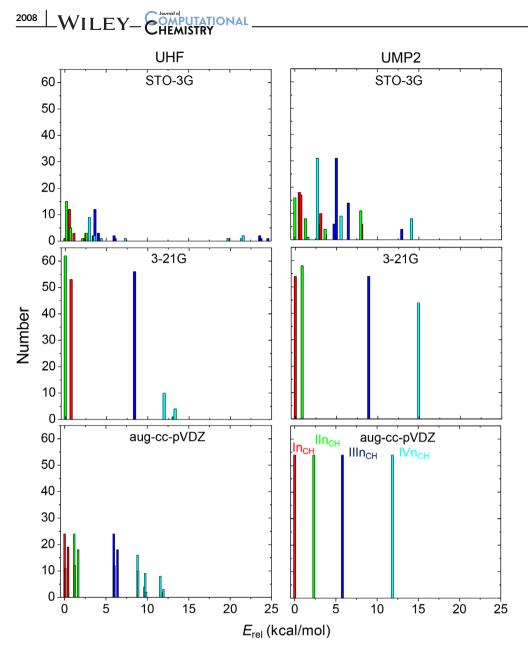[d]Frequency computation fails (imaginary frequencies are suspected).
[e]Imaginary frequencies are obtained.
[f]MOLPRO computations fail.

2.74, and 5.59 kcal/mol look like In$_{CH}$, In$_{CH}$, IVn$_{CH}$, and IVn$_{CH}$, respectively, in agreement with the assignments. However, it is important to note that all the conformers obtained at UMP2/STO-3G have large imaginary frequencies. Furthermore, in four cases the UMP2/STO-3G optimizations are not converged as seen in Table 2. Using the UHF method with the STO-3G basis each of the four conformers is obtained once and the other optimizations are not converged due to UHF convergence problems or the optimization procedure reaches a maximum of 100 steps. At the UHF/3-21G level four conformers are obtained, two optimizations fail, and the energy order of In$_{CH}$ and IIn$_{CH}$ reverses. Using UHF/aug-cc-pVDZ there is no convergence problem, but this level results in seven conformers (different energies) as In$_{CH}$ splits into 0.00 and 0.09 kcal/mol, IIIn$_{CH}$ into 5.94 and 6.04 kcal/mol, and IVn$_{CH}$ into 8.81 and 9.64 kcal/mol. There is no qualitative difference between the structures of the conformers which are assigned to the same minimum with UMP2/aug-cc-pVDZ.

In the case of the HN-CH$_2$-COOH radical, all the optimizations converge successfully (see Table 3). The UMP2/aug-cc-pVDZ level of theory results in 7 conformers, from which only two (IIIn$_{NH}$ and Vn$_{NH}$) do not have C_s symmetry as shown in Figure 3. The structures and energy order of the radical conformers are similar to the

corresponding parent glycine geometries as {Ip, IIn, IIIn, IVn, Vn, VIp, VIIp, VIIIn} result in {Ip$_{NH}$, IIp$_{NH}$, IIIn$_{NH}$, IVp$_{NH}$/Ip$_{NH}$, IIIn$_{NH}$/Vn$_{NH}$, VIp$_{NH}$, IIp$_{NH}$, VIIp$_{NH}$/VIp$_{NH}$}. The fact that the removal of different H atoms from the amino group of IVn, Vn, and VIIIn provides different radical conformers differing in the conformation of the NH group is expected considering the twisted orientation of the NH$_2$ group of these glycine conformers (see Figure 1). Comparing the structures of the eight glycine and seven radical conformers, one can notice that the VIIp-like radical conformer is missing as optimization initiated from VIIp results in IIp$_{NH}$, which has the same COOH conformation, but the NH group rotates into a favorable HN⋯HO arrangement, instead of the repulsive NH⋯HO. As Table 3 shows the lower levels of theory roughly give similar result; Ip$_{NH}$ is always the lowest energy conformer, the energy orders are similar, though IIp$_{NH}$ and IIIn$_{NH}$ as well as often IVp$_{NH}$ and Vn$_{NH}$ are reversed. VIIp$_{NH}$ is only obtained at the UHF/STO-3G, UHF/aug-cc-pVDZ, and UMP2/aug-cc-pVDZ levels, whereas using the other methods and bases the removal of both H atoms from VIIIn provides the energetically favored VIp$_{NH}$ conformer. Furthermore, at the UHF/STO-3G and UHF/3-21G levels some of the optimizations initiated from IIIn and Vn result in a C_s structure IIIp'$_{NH}$ (Figure 4), which is a transition state connecting two
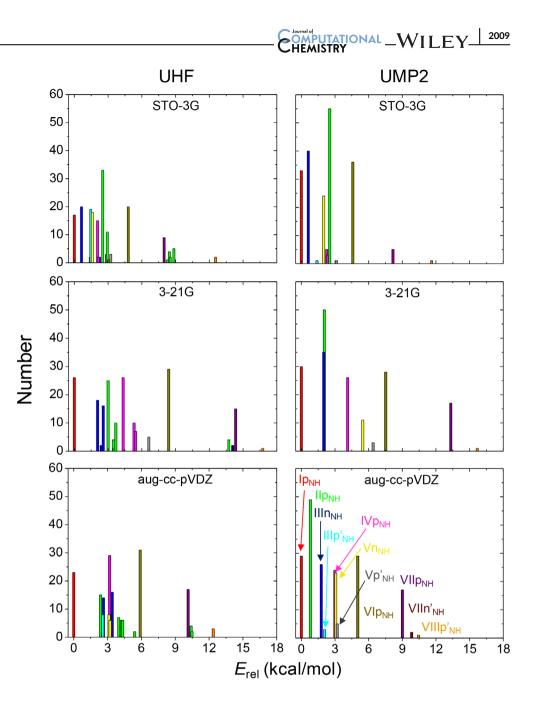
FIGURE 5 Number of the different initial geometries resulted in the same conformer with relative energy (E_{rel}) within 0.01 kcal/mol of H_2N-CH-COOH obtained from 216 initial structures at different levels of theory. The conformers (for structures see Figure 3) are assigned by UMP2/aug-cc-pVDZ computations initiated from the lower-level optimized structures [Color figure can be viewed at wileyonlinelibrary.com]

C_1 $IIIn_{NH}$ enantiomers. Thus, in the case of UHF/3-21G both $IIIn_{NH}$ and $VIIp_{NH}$ are missing. At the UMP2/STO-3G level one of the optimizations starting from $IIIn$ results in Ip_{NH} instead of $IIIn_{NH}$, nevertheless in this case $IIIn_{NH}$ is also obtained by removing the other H atom. Additional conformers (minima) are not found using the lower levels of theory.

For the H_2N-CH_2-COO radical MRCI/aug-cc-pVDZ finds four conformers as shown in Table 4 and Figure 3. There are two C_s conformers (Ip_{COO} and $IIIp_{COO}$), which differ in the conformation of the COO group, and there are two C_1 conformers (IIn_{COO} and IVn_{COO}), where the NH_2 group is twisted (Figure 3). (Note that an additional fifth conformer is also obtained from IIn, which seems to be a IVn_{COO}-like TS structure with C_s symmetry, but its saddle-point character cannot be confirmed, because the frequency computation does not converge for this conformer.) As shown in Table 4 Ip_{COO} is obtained from Ip and VIp at every level of theory, as expected, because these two glycine conformers have the same NH_2 and COO arrangements as

Ip_{COO}. IIn_{COO} is found by removing the hydroxyl H atom from IVn, again at every level of theory, due to the similar conformations. Considering structural similarity, we expect IIn_{COO} from $VIIIn$ as well, as we find using MRCI/aug-cc-pVDZ. However, the other levels either do not converge or result in Ip_{COO}, where the NH_2 group turns into an energetically favored symmetric orientation. In most cases we obtain $IIIp_{COO}$ from the structurally similar $IIIn$, except with the STO-3G basis, where new conformers are obtained that relax into Ip_{COO}. In the case of MCSCF/STO-3G the new conformer has an Ip_{COO}/$IIIp_{COO}$-like structure with twisted COO group (C_1 symmetry), which relaxes to Ip_{COO} at the MRCI/aug-cc-pVDZ level (Table 4). $IIIp_{COO}$ is also expected from the very similar and also planar $VIIp$, but this happens only at the MCSCF/STO-3G level, the other levels converge only with 3-21G resulting in IVn_{COO}, where the NH_2 group is twisted breaking the C_s symmetry. The conformation of IVn_{COO} is related to IIn and Vn, and indeed, the converged optimizations always result in IVn_{COO} from the dehydrogenated IIn and Vn. However, when

convergence problem does not occur and IVn_{COO} is obtained from both IIn and Vn, and in some cases from VIIp, the energies of the IVn_{COO}-like conformers are always different (see Table 4). Thus, additional conformers, which are IVn_{COO}-like minima at the lowest energies and C_s saddle points or twisted C_1 minimum (MCSCF/STO-3G) at the higher energies (highest energy MRCI/3-21G conformer has no symmetry with a twisted COO group), are found at lower levels of theory, which all result in the same IVn_{COO} conformer with further MRCI/aug-cc-pVDZ optimizations.

3.2.2 | Strategy II

Starting geometry optimizations from the 216 initial structures using the UMP2 method with the aug-cc-pVDZ basis set results in four different $H_2N-CH-COOH$ conformers with equal probability as shown in Figure 5. These conformers are the same as the ones obtained from Strategy I and shown in Figure 3. At the UMP2/3-21G level again the same four conformers are obtained with similar probability showing that the well around each minimum covers similar size of the configuration space. At the UMP2/STO-3G, UHF/STO-3G, UHF/3-21G, and UHF/aug-cc-pVDZ levels of theory the configuration space is more structured resulting in 18, 25, 7, and 17 conformers, respectively. The conformers, which were found with Strategy I are usually obtained with the highest probabilities. If we further optimize the above conformers using the UMP2/aug-cc-pVDZ level, all of them converge to the above-mentioned four different minimum structures as shown in Figure 5; thus, we can be confident that at higher level of theory four conformers of $H_2N-CH-COOH$ exist and Strategy II does not reveal any new conformer beyond the ones found via Strategy I.
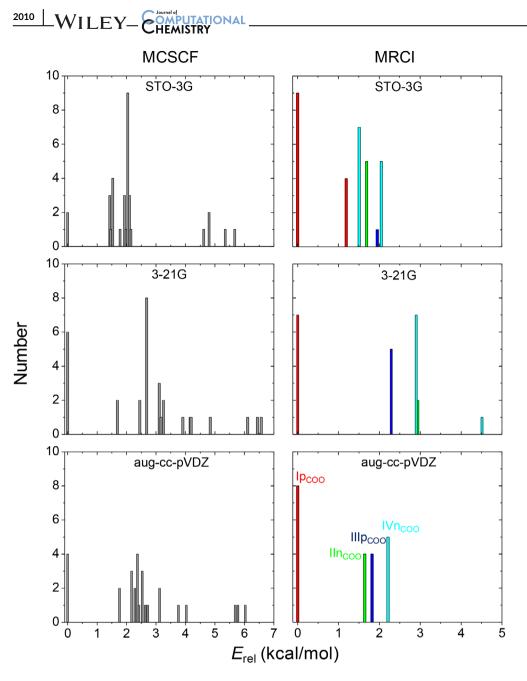
FIGURE 7 Number of the different initial geometries resulted in the same conformer with relative energy (E_{rel}) within 0.01 kcal/mol of H_2N-CH_2-COO obtained from 36 initial structures at different levels of theory. The MRCI conformers (for structures see Figure 3) are assigned by MRCI/aug-cc-pVDZ computations initiated from the lower-level optimized structures. The MCSCF conformers are not assigned [Color figure can be viewed at wileyonlinelibrary.com]

In the case of the HN-CH_2-COOH isomer, the Strategy II with UMP2/aug-cc-pVDZ provides seven conformers (minima) like Strategy I and four transition states (saddle points) as shown in Figure 6. The transition states, shown in Figure 4, connects the two enantiomer structures of $IIIn_{NH}$ and Vn_{NH} via $IIIp'_{NH}$ and Vp'_{NH} as mentioned earlier, $VIIn'_{NH}$ represents a COOH torsional barrier between $VIIp_{NH}$ and IIp_{NH}, and $VIIIp'_{NH}$ is the "missing" conformer with repulsive NH···HO arrangement, which turns out being a saddle point. These transition-state geometries, {$IIIp'_{NH}$, Vp'_{NH}, $VIIn'_{NH}$, $VIIIp'_{NH}$}, are obtained only {3, 5, 2, 1} times from the 216 initial structures as shown in Figure 6. The IIp_{NH} minimum is obtained 49 times, whereas the other minima are found about 20–30 times. The larger probability of the IIp_{NH} conformer can be explained by the fact that both IIn- and $VIIp$-like geometries result in IIp_{NH} as discussed at Strategy I (Table 3). The UMP2 method with the 3-21G and STO-3G basis sets basically provide the same seven conformers as in the case of the aug-cc-pVDZ basis. It is important to note that Strategy II

finds $VIIp_{NH}$ 17 and 5 times with 3-21G and STO-3G, respectively; whereas this conformer was missing using the above small basis sets with Strategy I. Using the UHF method the conformational potential is more rugged resulting in many conformers; some of them correspond to the ones found with Strategy I and the other usually have small probabilities as shown in Figure 6. These small probability conformers vanish with further optimizations at the UMP2/aug-cc-pVDZ level and at the end all the conformers relax to the structures shown in Figures 3 and 4.

For H_2N-CH_2-COO the 36 optimizations provide 4 conformers at the MRCI/aug-cc-pVDZ level of theory as shown in Figure 7. The conformers {Ip_{COO}, IIn_{COO}, $IIIp_{COO}$, IVn_{COO}} are obtained {8, 4, 4, 5} times, whereas 15 optimizations fail due to convergence problems. MRCI/3-21G gives 5 conformers, but the two different structures at 2.91 and 4.52 kcal/mol both converge to the same IVn_{COO} conformer at the MRCI/aug-cc-pVDZ level. Interestingly, Strategy I found a sixth conformer at 3.43 kcal/mol, which was also assigned to IVn_{COO}; however,

TABLE 5 Classical and adiabatic relative energies (kcal/mol) of the H_2N-CH-COOH conformers obtained at different levels of theory[a]

	Classical			ΔZPE		Adiabatic[b]		
	MP2/ aVDZ	CCSD(T)-F12b/aVDZ	CCSD(T)-F12b/aVTZ	MP2/ aVDZ	CCSD(T)-F12b/aVDZ	MP2/ aVDZ	CCSD(T)-F12b/aVDZ	CCSD(T)-F12b/ aVTZ[c]
In_{CH}	0.00	0.00	0.00	+0.00	+0.00	0.00	0.00	0.00
IIn_{CH}	2.32	1.52	1.57	+0.07	−0.02	2.39	1.50	1.55
$IIIn_{CH}$	5.80	5.26	5.25	−0.35	−0.22	5.45	5.03	5.03
IVn_{CH}	11.85	9.77	9.85	+0.28	−0.13	12.14	9.64	9.72

[a]Results correspond to optimized geometries obtained by UMP2/aug-cc-pVDZ, UCCSD(T)-F12b/aug-cc-pVDZ, and UCCSD(T)-F12b/aug-cc-pVTZ.
[b]Classical relative energy plus zero-point energy correction (ΔZPE).
[c]UCCSD(T)/aug-cc-pVTZ classical relative energy plus UCCSD(T)/aug-cc-pVDZ ΔZPE.

TABLE 6 Classical and adiabatic relative energies (kcal/mol) of the HN-CH_2-COOH conformers obtained at different levels of theory[a]

	Classical			ΔZPE		Adiabatic[b]		
	MP2/ aVDZ	CCSD(T)-F12b/aVDZ	CCSD(T)-F12b/aVTZ	MP2/ aVDZ	CCSD(T)-F12b/aVDZ	MP2/ aVDZ	CCSD(T)-F12b/aVDZ	CCSD(T)-F12b/ aVTZ[c]
Ip_{NH}	0.00	0.00	0.00	+0.00	+0.00	0.00	0.00	0.00
IIp_{NH}	0.81	0.74	0.78	+0.34	+0.28	1.15	1.02	1.06
$IIIn_{NH}$	1.78	1.90	1.93	+0.15	+0.15	1.93	2.04	2.08
IVp_{NH}	2.98	3.25	3.34	−0.06	−0.19	2.92	3.06	3.16
Vn_{NH}	3.08	3.30	3.39	+0.04	−0.10	3.12	3.20	3.29
VIp_{NH}	5.03	4.97	5.00	−0.18	−0.14	4.85	4.83	4.86
$VIIp_{NH}$	9.01	9.16	9.27	−0.31	−0.40	8.70	8.75	8.87

[a]Results correspond to optimized geometries obtained by UMP2/aug-cc-pVDZ, UCCSD(T)-F12b/aug-cc-pVDZ, and UCCSD(T)-F12b/aug-cc-pVTZ.
[b]Classical relative energy plus zero-point energy correction (ΔZPE).
[c]UCCSD(T)/aug-cc-pVTZ classical relative energy plus UCCSD(T)/aug-cc-pVDZ ΔZPE.

TABLE 7 Classical and adiabatic relative energies (kcal/mol) of the HN-CH_2-COOH transition states obtained at different levels of theory[a]

	Classical			ΔZPE		Adiabatic[b]		
	MP2/ aVDZ	CCSD(T)-F12b/aVDZ	CCSD(T)-F12b/aVTZ	MP2 /aVDZ	CCSD(T)-F12b/aVDZ	MP2/ aVDZ	CCSD(T)-F12b/aVDZ	CCSD(T)-F12b/ aVTZ[c]
$IIIp'_{NH}$	2.08	2.25	2.25	+0.21	−0.19	2.29	2.06	2.06
Vp'_{NH}	3.20	3.42	3.53	+0.55	−0.13	3.75	3.29	3.40
$VIIn'_{NH}$	9.83	10.01	10.08	+0.36	−0.33	10.19	9.69	9.75
$VIIIp'_{NH}$	10.45	10.41	10.40	+0.14	−0.78	10.59	9.63	9.62

[a]Results correspond to optimized geometries obtained by UMP2/aug-cc-pVDZ, UCCSD(T)-F12b/aug-cc-pVDZ, and UCCSD(T)-F12b/aug-cc-pVTZ.
[b]Classical relative energy plus zero-point energy correction (ΔZPE).
[c]UCCSD(T)/aug-cc-pVTZ classical relative energy plus UCCSD(T)/aug-cc-pVDZ ΔZPE.

this sixth conformer is not seen with Strategy II. Using MRCI/STO-3G six conformers are obtained, which all assigned to the same four minima with further MRCI/aug-cc-pVDZ optimizations as shown in Figure 7. Strategy I gave four conformers at the MRCI/STO-3G level, but $IIIp_{COO}$ was missing, which is found with Strategy II, albeit only once. Furthermore, Strategy II finds an additional conformer at 2.05 kcal/mol, which is assigned to IVn_{COO}. In the case of the MCSCF method 14, 14, and 15 conformers are found with the STO-3G, 3-21G, and aug-cc-pVDZ basis sets, respectively, showing again that the potential energy surface is more structured at lower levels of theory. Here many conformers are found only 1 or 2 times from the 36 optimizations, and only a few of

them, which were also obtained with Strategy I, are found 4–9 times. Owing to the large number of conformers, we do not perform MRCI/ aug-cc-pVDZ optimization for each geometry, nevertheless, on the basis of our previous findings we assume that all these conformers would result in the same four minima as seen using MRCI (Figure 7).

3.2.3 | Benchmark structures and energies

The high-level UCCSD(T)-F12b geometry optimizations with the aug-cc-pVDZ and aug-cc-pVTZ basis sets, initiated from the UMP2/

TABLE 8 Classical and adiabatic relative energies (kcal/mol) of the H_2N-CH_2-COO conformers obtained with MRCI, MRCI+Q, and MRCI-F12+Q using the aug-cc-pVDZ basis set

	Classical[a]			ΔZPE	Adiabatic[b]		
	MRCI	MRCI+Q	MRCI-F12+Q	MRCI	MRCI	MRCI+Q[c]	MRCI-F12+Q[d]
Ip_{COO}	0.00	0.00	0.00	+0.00	0.00	0.00	0.00
IIn_{COO}	1.64	1.61	1.65	−0.01	1.63	1.60	1.64
$IIIp_{COO}$	1.82	1.78	1.78	−0.03	1.79	1.75	1.75
IVn_{COO}	2.21	2.21	2.21	+0.00	2.21	2.21	2.21

[a]Results correspond to optimized geometries obtained by MRCI/aug-cc-pVDZ.
[b]Classical relative energy plus zero-point energy correction (ΔZPE).
[c]MRCI+Q/aug-cc-pVDZ classical relative energy plus MRCI/aug-cc-pVDZ ΔZPE.
[d]MRCI-F12+Q/aug-cc-pVDZ classical relative energy plus MRCI/aug-cc-pVDZ ΔZPE.

TABLE 9 Classical and adiabatic relative energies (kcal/mol) of the dehydrogenated glycine conformers obtained with the MRCI+Q, MRCI-F12+Q, and UCCSD(T)-F12b methods

	Classical[a]			Adiabatic[b]		
	MRCI+Q	MRCI-F12+Q	CCSD(T)-F12b	MRCI+Q	MRCI-F12+Q	CCSD(T)-F12b
In_{CH}	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
IIn_{CH}	1.62 (1.62)	1.71 (1.71)	1.57 (1.57)	1.60 (1.60)	1.69 (1.69)	1.55 (1.55)
$IIIn_{CH}$	5.35 (5.35)	5.58 (5.58)	5.25 (5.25)	5.12 (5.12)	5.36 (5.36)	5.03 (5.03)
IVn_{CH}	9.67 (9.67)	10.24 (10.24)	9.85 (9.85)	9.54 (9.54)	10.11 (10.11)	9.72 (9.72)
Ip_{NH}	16.66 (0.00)	18.51 (0.00)	21.20 (0.00)	15.47 (0.00)	17.32 (0.00)	20.01 (0.00)
IIp_{NH}	17.90 (1.25)	19.84 (1.33)	21.98 (0.78)	16.99 (1.53)	18.93 (1.61)	21.07 (1.06)
$IIIn_{NH}$	18.59 (1.93)	20.61 (2.11)	23.13 (1.93)	17.55 (2.08)	19.58 (2.26)	22.09 (2.08)
IVp_{NH}	19.66 (3.00)	21.81 (3.30)	24.54 (3.34)	18.28 (2.81)	20.43 (3.11)	23.17 (3.16)
Vn_{NH}	19.70 (3.05)	21.89 (3.39)	24.59 (3.39)	18.42 (2.95)	20.61 (3.29)	23.30 (3.29)
VIp_{NH}	21.68 (5.02)	23.77 (5.27)	26.19 (5.00)	20.35 (4.88)	22.45 (5.13)	24.87 (4.86)
$VIIp_{NH}$	25.64 (8.99)	28.11 (9.60)	30.47 (9.27)	24.05 (8.59)	26.52 (9.20)	28.88 (8.87)
Ip_{COO}	29.18 (0.00)	31.88 (0.00)		28.96 (0.00)	31.66 (0.00)	
IIn_{COO}	30.79 (1.61)	33.53 (1.65)		30.56 (1.60)	33.31 (1.64)	
$IIIp_{COO}$	30.96 (1.78)	33.65 (1.78)		30.71 (1.75)	33.41 (1.75)	
IVn_{COO}	31.39 (2.21)	34.09 (2.21)		31.17 (2.21)	33.87 (2.21)	

[a]Classical MRCI+Q/aug-cc-pVDZ, MRCI-F12+Q/aug-cc-pVDZ, and UCCSD(T)-F12b/aug-cc-pVTZ relative energies at UCCSD(T)-F12b/aug-cc-pVTZ (H_2N-CH-COOH and HN-CH_2-COOH) and MRCI/aug-cc-pVDZ (H_2N-CH_2-COO) geometries.
[b]Classical MRCI+Q/aug-cc-pVDZ, MRCI-F12+Q/aug-cc-pVDZ, and UCCSD(T)-F12b/aug-cc-pVTZ relative energies plus UCCSD(T)-F12b/aug-cc-pVDZ (H_2N-CH-COOH and HN-CH_2-COOH) and MRCI/aug-cc-pVDZ (H_2N-CH_2-COO) zero-point energy corrections.

aug-cc-pVDZ conformers, give four minima for H_2N-CH-COOH and seven minima (and four transition states) for HN-CH_2-COOH; thus, none of the UMP2/aug-cc-pVDZ conformers disappears at higher levels of theory. As Table 5 shows the MP2/aug-cc-pVDZ level significantly overestimates the relative energies of the H_2N-CH-COOH conformers as the UCCSD(T)-F12b/aug-cc-pVDZ data are lower by 0.80, 0.54, and 2.08 kcal/mol for IIn_{CH}, $IIIn_{CH}$, and IVn_{CH}, respectively. The UCCSD(T)-F12b relative energies with the aug-cc-pVDZ and aug-cc-pVTZ basis sets agree within 0.05 (IIn_{CH}), 0.01 ($IIIn_{CH}$), and 0.08 (IVn_{CH}) kcal/mol, showing the excellent basis-set-convergence of the explicitly-correlated UCCSD(T)-F12b method. The benchmark (UCCSD(T)-F12b/aug-cc-pVTZ) relative energies of the $\{In_{CH}, IIn_{CH}, IIIn_{CH}, IVn_{CH}\}$ conformers are {0.00, 1.57, 5.25, 9.85} kcal/mol. Applying UCCSD(T)-F12b/aug-cc-pVDZ ZPE corrections of {0.00, −0.02, −0.22, −0.13} kcal/mol, we obtain the following

benchmark adiabatic relative energies: {0.00, 1.55, 5.03, 9.72} kcal/mol.

The best classical and adiabatic relative energies of the HN-CH_2-COOH conformers are given in Table 6 (minima) and Table 7 (transition states). Here UMP2/aug-cc-pVDZ fortuitously provides reasonably accurate relative energies with only 0.1–0.2 kcal/mol deviations from the UCCSD(T)-F12b/aug-cc-pVDZ data (the maximum difference is 0.27 kcal/mol for IVp_{NH}). UCCSD(T)-F12b again shows rapid convergence; thus, the final UCCSD(T)-F12b/aug-cc-pVTZ classical relative energies are definitely basis-set converged within ±0.1 kcal/mol or better. The ZPE corrections are between −0.4 and +0.3 kcal/mol for the minima and −0.8 and −0.1 kcal/mol for the transition states as shown in Tables 6 and 7, respectively. The relative energies of the seven conformers span a roughly 10 kcal/mol range, and the energy order is the same with UMP2/aug-cc-pVDZ, UCCSD(T)-F12b/

aug-cc-pVDZ, and UCCSD(T)/aug-cc-pVTZ regardless ZPE correction. The classical energy of the $IIIp'_{NH}$ transition state is above the energy of $IIIn_{NH}$ by 0.30, 0.35, and 0.32 kcal/mol at the UMP2/aug-cc-pVDZ, UCCSD(T)-F12b/aug-cc-pVDZ, and UCCSD(T)/aug-cc-pVTZ levels, respectively, whereas the corresponding adiabatic energy differences are 0.36, 0.02, and −0.02 kcal/mol. Thus, classically the nonsymmetric $IIIn_{NH}$ structure is clearly favored, whereas the ZPE-corrected energies of $IIIn_{NH}$ and $IIIp'_{NH}$ are almost the same at the highest levels of theory. In the case of Vp'_{NH} versus Vn_{NH}, the classical energies show a low barrier of about 0.1 kcal/mol and the adiabatic barrier heights are also positive about 0.7 kcal/mol (UMP2) and 0.1–0.2 kcal/mol (UCCSD(T)-F12b). $VIIn'_{NH}$ is clearly above $VIIp_{NH}$ by 0.8–0.9 kcal/mol classically and 0.8–1.5 kcal/mol adiabatically and $VIIIp'_{NH}$ has significantly higher energy than any other conformer of $HN-CH_2-COOH$.

The four conformers of the H_2N-CH_2-COO radical are very close to each other in energy, as the classical(adiabatic) relative energies of $\{Ip_{COO}, IIn_{COO}, IIIp_{COO}, IVn_{COO}\}$ are $\{0.00(0.00), 1.64(1.63), 1.82(1.79), 2.21(2.21)\}$ kcal/mol at the MRCI/aug-cc-pVDZ level of theory as shown in Table 8. The Davidson corrections (+Q), which estimate the dynamical correlation effects beyond double excitations, are found to be small (0.00–0.04 kcal/mol) as seen in Table 8. Furthermore, the basis-set effects beyond aug-cc-pVDZ are also negligible, because the standard MRCI+Q and explicitly correlated MRCI-F12+Q relative energies again agree within 0.00–0.04 kcal/mol (Table 8).

Comparison of the benchmark classical and adiabatic energies of all the conformers of the $H_2N-CH-COOH$, $HN-CH_2-COOH$, and H_2N-CH_2-COO radicals is shown in Table 9. The lowest energy conformer is In_{CH}; the classical(adiabatic) MRCI-F12+Q energies of Ip_{NH} and Ip_{COO} are 18.51(17.32) and 31.88(31.66) kcal/mol relative to In_{CH}, respectively. The energies of all the conformers of $H_2N-CH-COOH$ are below the energy of Ip_{NH} and all the $HN-CH_2-COOH$ conformers are below Ip_{COO}. Thus, we can conclude that H abstraction is thermodynamically preferred from the CH_2 group of glycine, followed by the H abstraction from the amino and carboxyl groups in increasing energy order. For the conformers of $H_2N-CH-COOH$ and $HN-CH_2-COOH$ both MRCI (specifically MRCI+Q and MRCI-F12+Q) and CCSD(T)-F12b relative energies are available, which are in good agreement with only about 0.2 kcal/mol mean and 0.6 kcal/mol maximum absolute deviations if we consider the energies of the conformers relative to In_{CH} and Ip_{NH}, respectively. However, for the classical(adiabatic) energy gap between the In_{CH} and Ip_{NH} conformers, MRCI+Q, MRCI-F12+Q, and CCSD(T)-F12b give 16.66(15.47), 18.51 (17.32), and 21.20(20.01) kcal/mol, respectively. Considering the energy difference between In_{CH} and Ip_{COO}, the MRCI+Q and MRCI-F12+Q classical(adiabatic) results are 29.18(28.96) and 31.88(31.66) kcal/mol, respectively, which are above the corresponding energies of 25.64(24.05) and 28.11(26.52) kcal/mol of the highest-energy conformer of $HN-CH_2-COOH$ ($VIIp_{NH}$), whereas the CCSD(T)-F12b energy of $VIIp_{NH}$, 30.47(28.88) kcal/mol, is, in the classical case, slightly above the MRCI+Q energy of Ip_{COO}. Nevertheless, the presumably the more accurate MRCI-F12+Q energy of Ip_{COO} is clearly above the CCSD(T)-F12b energy of $VIIp_{NH}$.

4 | SUMMARY AND CONCLUSIONS

We have determined the first explicitly-correlated CCSD(T)-F12b/ aug-cc-pVTZ structures and relative energies of the eight conformers of glycine confirming the predictions of previous studies.[1,4] Furthermore, we report a comprehensive ab initio investigation of the conformers and isomers of dehydrogenated glycine radicals revealing 4, 7 (+4 TS), and 4 conformers for $H_2N-CH-COOH$, $HN-CH_2-COOH$, and H_2N-CH_2-COO, respectively. The four conformers of $H_2N-CH-COOH$ are nonsymmetric (C_1), whereas the conformers of the other two isomers have either C_1 or C_s point-group symmetry.

We have used two different strategies for the conformation search employing various ab initio methods and basis sets. Strategy I is motivated by chemical intuition suggesting initial geometries by removing different H atoms from the eight known conformers of glycine. Strategy II systematically maps the conformational space of the glycine radicals generating initial structures for geometry optimizations by scanning the most important torsional coordinates with 60° steps as was previously done for the amino acid threonine.[39] The conclusions of the detailed search using the different strategies and ab initio levels can be summarized as follows:

1. Strategy I often finds all the conformers. ($VIIp_{NH}$ is not obtained at UHF/3-21G, UMP2/STO-3G, and UMP2/3-21G; IVn_{COO} is not found at MCSCF/aug-cc-pVDZ; $IIIp_{COO}$ is missing at MRCI/ STO-3G.)

2. The conformational space is usually more structured at the UHF and MCSCF levels than with the UMP2 and MRCI methods. However, the additional conformers found at the lower levels of theory disappear when further optimizations are performed using higher-level correlation methods.

3. Strategy II with the UMP2 and MRCI methods provides qualitatively the same conformers with the 3-21G and aug-cc-pVDZ basis sets, whereas the small STO-3G basis predicts additional conformers, which converge to the known minima with larger basis sets.

4. Both Strategies I and II give the same conformers at UMP2/aug-cc-pVDZ ($H_2N-CH-COOH$ and $HN-CH_2-COOH$) and MRCI/aug-cc-pVDZ (H_2N-CH_2-COO) levels of theory.

5. All the conformers found at the UMP2/aug-cc-pVDZ level of theory can be confirmed using the CCSD(T)-F12b method with the aug-cc-pVDZ and aug-cc-pVTZ basis sets.

6. For larger systems we recommend the initial conformational search at a computationally cheap low-level of theory using either Strategy I or II, followed by higher-level optimizations where several conformers are likely to disappear. In the case of Strategy II the MP2 method with the 3-21G basis is an economic choice, for the initial search there is no need for the larger aug-cc-pVDZ basis. Between 3-21G and aug-cc-pVDZ, one may consider using the 6-31G, 6-31G*, and 6-31+G* basis sets as well.

The present study focuses on ab initio methods; however, it is important to note that density functional theory may also become

useful for conformational searches of larger systems. For example, a recent study found excellent performance of the B3LYP-D3BJ and ωB97X-V functionals for the determination of conformational energies of amino acids with N- and C-termination.[40]

Benchmark MRCI-F12+Q[UCCSD(T)-F12b] ZPE-corrected computations show that the four conformers of H_2N-CH-COOH have the lowest energies in the 0.00–10.11[0.00–9.72] kcal/mol range, followed by the seven conformers of HN-CH_2-COOH in the energy range of 17.32–26.52[20.01–28.88] kcal/mol and the four conformers of H_2N-CH_2-COO in the range of 31.66–33.87 kcal/mol. We assume that the CCSD(T)-F12b results are more accurate, because CCSD(T)-F12b provides a better description of dynamical electron correlation, whereas static electron correlation is not significant for the H_2N-CH-COOH and HN-CH_2-COOH conformers as the T_1-diagnostic[41] values are only around 0.017. For the H_2N-CH_2-COO geometries, we have found convergence problems when using single-configuration methods; thus, in this case only multi-reference data could be obtained.

Besides the new benchmark properties and the first comprehensive characterization of the dehydrogenated glycine conformers, the present ab initio investigation opens the door for more detailed studies of the H-abstraction reactions of free radicals with glycine. Future work may consider solvation effects to mimic biological environment. Furthermore, the conformational search strategies could be used to find conformers of similar or even larger complex molecular systems.

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REFERENCES

[1] A. G. Császár, *J. Am. Chem. Soc.* **1992**, *114*, 9568.
[2] A. G. Császár, *J. Mol. Struct.* **1995**, *346*, 141.
[3] V. Kasalová, W. D. Allen, H. F. Schaefer III., E. Czinki, A. G. Császár, *J. Comput. Chem.* **2007**, *28*, 1373.
[4] R. M. Balabin, *Chem. Phys. Lett.* **2009**, *479*, 195.
[5] R. M. Balabin, *J. Phys. Chem. Lett.* **2010**, *1*, 20.
[6] R. M. Balabin, *Phys. Chem. Chem. Phys.* **2012**, *14*, 99.
[7] G. Bazsó, G. Magyarfalvi, G. Tarczay, *J. Mol. Struct.* **2012**, *1025*, 33.
[8] G. Bazsó, G. Magyarfalvi, G. Tarczay, *J. Phys. Chem. A* **2012**, *116*, 10539.
[9] V. Barone, M. Biczysko, J. Bloino, C. Puzzarini, *Phys. Chem. Chem. Phys.* **2013**, *15*, 1358.
[10] V. Barone, M. Biczysko, J. Bloino, C. Puzzarini, *Phys. Chem. Chem. Phys.* **2013**, *15*, 10094.
[11] S. Coussan, G. Tarczay, *Chem. Phys. Lett.* **2016**, *644*, 189.
[12] F. Gabas, R. Conte, M. Ceotto, *J. Chem. Theory Comput.* **2017**, *13*, 2378.
[13] D. Yu, A. Rauk, D. A. Armstrong, *J. Am. Chem. Soc.* **1995**, *117*, 1789.
[14] A. Galano, J. R. Alvarez-Idaboy, L. A. Montero, A. Vivier-Bunge, *J. Comput. Chem.* **2001**, *22*, 1138.
[15] A. K. Croft, C. J. Easton, L. Radom, *J. Am. Chem. Soc.* **2003**, *125*, 4119.
[16] Y. Huang, L. Guler, J. Heidbrink, H. Kenttämaa, *J. Am. Chem. Soc.* **2005**, *127*, 3973.
[17] A. Mavrandonakis, S. C. Farantos, G. E. Froudakis, *J. Phys. Chem. B* **2006**, *110*, 6048.
[18] G. Yang, G. Zu, L. Zhou, *J. Phys. Org. Chem.* **2008**, *21*, 34.
[19] P. Carbonniere, A. Dargelos, I. Ciofini, C. Adamo, C. Pouchan, *Phys. Chem. Chem. Phys.* **2009**, *11*, 4375.
[20] M. Liessmann, B. Hansmann, P. G. Blachly, J. S. Francisco, B. Abel, *J. Phys. Chem. A* **2009**, *113*, 7570.
[21] R.-J. Lin, C.-C. Wu, S. Jang, F.-Y. Li, *J. Mol. Model.* **2010**, *16*, 175.
[22] M. C. Owen, M. Szőri, I. G. Csizmadia, B. Viskolcz, *J. Phys. Chem. B* **2012**, *116*, 1143.
[23] J. Uranga, O. Lakuntza, E. Ramos-Cordoba, J. M. Matxain, J. I. Mujika, *Phys. Chem. Chem. Phys.* **2016**, *18*, 30972.
[24] M. C. Owen, I. G. Csizmadia, B. Viskolcz, B. Strodel, *Molecules* **2017**, *22*, 655.
[25] T. B. Adler, G. Knizia, H.-J. Werner, *J. Chem. Phys.* **2007**, *127*, 221106.
[26] C. Møller, M. S. Plesset, *Phys. Rev.* **1934**, *46*, 618.
[27] T. H. Dunning Jr., *J. Chem. Phys.* **1989**, *90*, 1007.
[28] J. A. Pople, R. K. Nesbet, *J. Chem. Phys.* **1954**, *22*, 571.
[29] R. D. Amos, J. S. Andrews, N. C. Handy, P. J. Knowles, *Chem. Phys. Lett.* **1991**, *185*, 256.
[30] W. J. Hehre, R. F. Stewart, J. A. Pople, *J. Chem. Phys.* **1969**, *51*, 2657.
[31] J. S. Binkley, J. A. Pople, W. J. Hehre, *J. Am. Chem. Soc.* **1980**, *102*, 939.
[32] W. J. Hehre, L. Radom, P. V. R. Schleyer, J. A. Pople, *Molecular Orbital Theory*, Wiley, New York **1986**.
[33] H.-J. Werner, P. J. Knowles, *J. Chem. Phys.* **1985**, *82*, 5053.
[34] H.-J. Werner, P. J. Knowles, *J. Chem. Phys.* **1988**, *89*, 5803.
[35] G. Knizia, T. B. Adler, H.-J. Werner, *J. Chem. Phys.* **2009**, *130*, 054104.
[36] S. R. Langhoff, E. R. Davidson, *Int. J. Quantum Chem.* **1974**, *8*, 61.
[37] T. Shiozaki, G. Knizia, H.-J. Werner, *J. Chem. Phys.* **2011**, *134*, 034113.
[38] MOLPRO, version 2015.1, a package of *ab initio* programs, H.-J. Werner, P. J. Knowles, G. Knizia, F. R. Manby, M. Schütz and others, see http://www.molpro.net.
[39] T. Szidarovszky, G. Czakó, A. G. Császár, *Mol. Phys.* **2009**, *107*, 761.
[40] M. K. Kesharwani, A. Karton, J. M. L. Martin, *J. Chem. Theory Comput.* **2016**, *12*, 444.
[41] T. J. Lee, P. R. Taylor, *Int. J. Quant. Chem.* **1989**, *S23*, 199.

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