

# Benchmark ab initio proton affinity and gas-phase basicity of $\alpha$ -alanine based on coupled-cluster theory and statistical mechanics

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## Abstract

We determine the proton affinity (PA) and gas-phase basicity (GB) of amino acid  $\alpha$ -alanine at a chemically accurate level by performing explicitly-correlated CCSD(T)-F12b/aug-cc-pVDZ geometry optimizations and normal mode vibrational frequency calculations as well as CCSD(T)-F12b/aug-cc-pVTZ energy computations at the possible neutral and protonated geometries. Temperature effects at 298.15 K considering translational, rotational, and vibrational enthalpy and entropy corrections are obtained via standard statistical mechanics utilizing the molecular geometries and the harmonic vibrational energy levels. Both the amino nitrogen (N) and the carbonyl oxygen (O) atoms are proven to be potential protonation sites and a systematic conformational search reveals 3 N- and 9 O-protonated conformers in the 0.00–7.88 and 25.43–30.43 kcal/mol energy ranges at 0 K, respectively. The final computed PA and GB values at (0)298.15 K in case of N-protonation are (214.47)216.80 and 207.07 kcal/mol, respectively, whereas the corresponding values for O-protonation are (189.04)190.63 and 182.31 kcal/mol. The results of the benchmark high-level coupled-cluster computations are utilized to assess the accuracy of several lower-level cost-effective methods such as MP2 and density functional theory with various functionals (SOGGA11-X, M06-2X, PBE0, B3LYP, M06, TPSS).

## KEYWORDS

ab initio thermochemistry, amino acid, conformational equilibrium, gas-phase basicity, proton affinity, statistical mechanics,  $\alpha$ -alanine

## 1 | INTRODUCTION

Conformers of amino acids are widely studied in the gas phase by both experimental and theoretical methods.<sup>1–20</sup> It is well established in the literature that the simplest amino acid, glycine ( $\text{H}_2\text{N}-\text{CH}_2-\text{COOH}$ ), has eight conformers (minima on the potential energy surface), three with  $C_s$  and five with  $C_1$  symmetry.<sup>1</sup> Replacing an H atom of the  $\text{CH}_2$  group of glycine with a methyl ( $\text{CH}_3$ ) group, one can derive  $3 + 2 \times 5 = 13$   $\alpha$ -alanine ( $\text{H}_2\text{N}-\text{CH}(\text{CH}_3)-\text{COOH}$ ) conformers, whose structures and relative energies are also well known in the literature.<sup>2,4</sup> Two of the important thermochemical quantities of amino

acids are their proton affinities (PAs) and gas-phase basicities (GBs).<sup>21–35</sup> In order to determine the PA and GB values using first-principles theoretical methods, one needs to know the structures, energies, and vibrational frequencies of both the neutral amino acid and its protonated form. Furthermore, like the neutral amino acids, their protonated counterparts may also have several conformers, whose knowledge is also required to compute reliable PAs and GBs at finite temperatures. However, the comprehensive investigations of the conformers of protonated amino acids are less widespread than those of the neutral amino acids. For glycine, we recently reported three amino (N) protonated and eight carbonyl (O) protonated glycine

conformers,<sup>36</sup> following the old work of Zhang and Chung-Phillips,<sup>37</sup> who found three and five conformers, respectively. For the other amino acids, PA and GB studies usually consider the presumably lowest-energy protonated conformers focusing on the energetically favored N-protonation.<sup>23,26,30,32,35</sup> Even in the case of alanine, we are not aware of any comprehensive conformational search for protonated species, only one theoretical work reported 2 O-protonated  $\alpha$ -alanine conformers besides an N-protonated one.<sup>38</sup> Furthermore, most of the previous studies used low-level electronic structure methods such as Hartree–Fock, MP2, and density functional theory (DFT) with modest basis sets to determine protonated alanine structures and energies as well as PA and GB values.<sup>23,24,26,32–34</sup> Therefore, in the present work we plan to perform a systematic conformational search for N- and O-protonated  $\alpha$ -alanine using the MP2 method, followed by high-level explicitly-correlated CCSD(T)-F12b computations. We also optimize the geometries of the 13  $\alpha$ -alanine conformers using the CCSD(T)-F12b method, thereby providing the first coupled-cluster structures and frequencies for this amino acid. Utilizing the high-level energies, frequencies, and structural parameters of the neutral and protonated  $\alpha$ -alanine conformers, we determine benchmark PA and GB values using standard statistical mechanics. Furthermore, the new benchmark data allow assessing the accuracy of lower-level DFT and MP2 methods, which may be utilized for larger systems.

In Section 2 and in the Supporting Information we describe the computational methods and details of the *ab initio* and DFT conformer search, the numerical geometric comparisons of the conformers, which may be utilized for larger, more complicated systems as well, and the statistical mechanics used to determine the thermal corrections for PA and GB. In Section 3 we discuss the results on the neutral, N- and O-protonated  $\alpha$ -alanine conformers as well as the PA and GB values, and compare the DFT results with the benchmark coupled-cluster values. Furthermore, we test the performance of the different variants of the CCSD(T)-F12 method with various correlation-consistent basis sets and the benchmark PA and GB are also compared to a collection of experimental data taken from the literature. The paper ends with summary and conclusions in Section 4.

## 2 | METHODS AND COMPUTATIONAL DETAILS

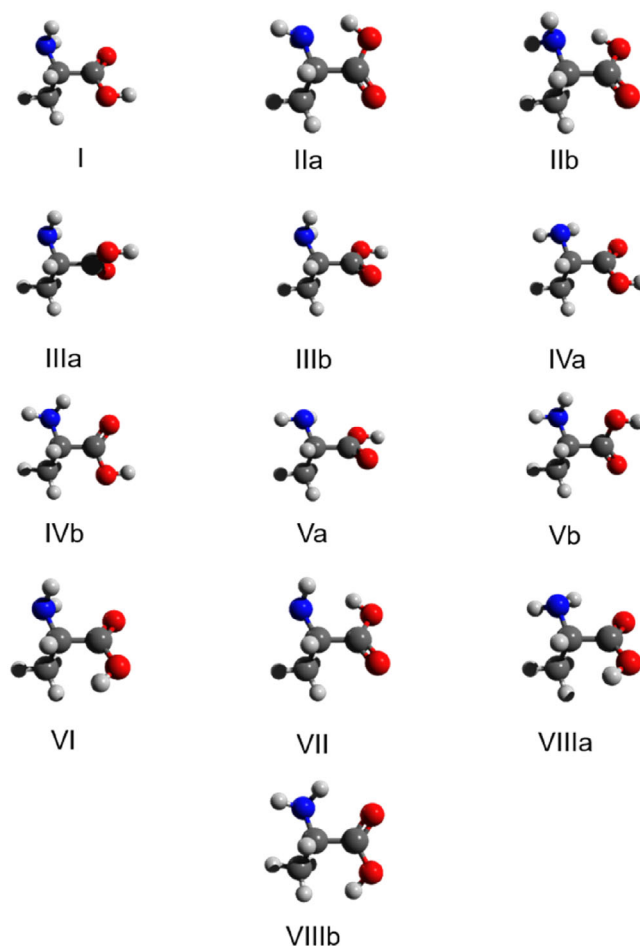
### 2.1 | *Ab initio* and DFT conformer search

The structures and harmonic vibrational frequencies of the 13 conformers of  $\alpha$ -alanine are obtained using the second-order Møller–Plesset perturbation (MP2)<sup>39</sup> and the explicitly-correlated coupled-cluster singles, doubles, and perturbative triples (CCSD(T)-F12b)<sup>40</sup> methods with the correlation-consistent aug-cc-pVDZ basis set<sup>41</sup> based on the tabular geometry data (MP2/6–311++G\*\*) provided by the early work of Császár.<sup>2</sup>

N-protonated  $\alpha$ -alanines are derived from the MP2/aug-cc-pVDZ optimized neutral conformer, I, with the lowest classical energy. Ia-N

is obtained by the protonation of I followed by geometry optimization. Then, a systematic search is performed by changing the dihedral angles of Ia-N. For the methyl and protonated amino groups, the combinations of eclipsed and staggered positions relative to the  $\alpha$ -hydrogen are considered, while the carboxyl group is completely rotated in the *cis* and *trans* positions with 60-degree increments. Thus, the number of initial geometries is 48 ( $2 \times 2 \times 2 \times 6$ ).

The conformer I of neutral  $\alpha$ -alanine at MP2/aug-cc-pVDZ level of theory is also considered as a starting point in the systematic search of O-protonated conformers. By varying the dihedral angles of the amino-, methyl-, protonated carboxyl-, and hydroxyl groups 144 ( $6 \times 2 \times 3 \times 2 \times 2$ ) different initial geometries are generated, at which geometry optimizations are performed. The amino group is completely rotated in 60-degree increments (6 positions). The methyl group is also rotated in such increments, however, due to symmetry only eclipsed and staggered positions relative to the  $\alpha$ -hydrogen are given (two positions). Due to similar symmetry related considerations, the protonated carboxyl group is rotated halfway in 60-degree increments (three positions). For the hydroxyl groups of  $\text{C}(\text{OH})_2^+$ , combinations of *cis* and *trans* structures were investigated due to planar geometry ( $2 \times 2$  positions). Conformers are collected exclusively from



**FIGURE 1** Conformers of neutral  $\alpha$ -alanine obtained at the CCSD(T)-F12b/aug-cc-pVDZ level of theory

**TABLE 1** Thermodynamic properties of gas-phase neutral  $\alpha$ -alanines at the CCSD(T)-F12b/aug-cc-pVTZ//CCSD(T)-F12b/aug-cc-pVDZ level ( $T = 298.15$  K,  $p = 100,000$  Pa)

| Conformer | $\Delta E_{\text{e,rel}}^a$ | $\Delta H_{0,\text{rel}}^a$ | $\Delta H_{\text{rel}}^{\circ a}$ | $\Delta G_{\text{rel}}^{\circ a}$ | $\Delta S^{\circ b}$ | $x^{\circ c}$ |
|-----------|-----------------------------|-----------------------------|-----------------------------------|-----------------------------------|----------------------|---------------|
| I         | 0.00                        | 0.00                        | 0.00                              | 0.00                              | 80.99                | 0.4414        |
| IIa       | 0.30                        | 0.56                        | 0.41                              | 0.67                              | 80.12                | 0.1433        |
| IIb       | 0.11                        | 0.44                        | 0.26                              | 0.71                              | 79.49                | 0.1331        |
| IIIa      | 1.27                        | 1.57                        | 1.45                              | 1.70                              | 80.15                | 0.0248        |
| IIIb      | 1.23                        | 1.28                        | 1.26                              | 1.23                              | 81.11                | 0.0557        |
| IVa       | 1.13                        | 1.01                        | 1.01                              | 1.03                              | 80.93                | 0.0774        |
| IVb       | 1.25                        | 1.09                        | 1.07                              | 1.10                              | 80.90                | 0.0694        |
| Va        | 2.25                        | 2.13                        | 2.13                              | 2.12                              | 81.04                | 0.0124        |
| Vb        | 1.76                        | 1.54                        | 1.55                              | 1.39                              | 81.53                | 0.0421        |
| VI        | 4.95                        | 4.72                        | 4.79                              | 4.65                              | 81.47                | 0.0002        |
| VII       | 5.68                        | 5.43                        | 5.39                              | 5.44                              | 80.81                | 0.0000        |
| VIIIa     | 6.03                        | 5.77                        | 5.80                              | 5.79                              | 81.00                | 0.0000        |
| VIIIb     | 6.15                        | 5.83                        | 5.84                              | 5.66                              | 81.60                | 0.0000        |

<sup>a</sup>Energy related quantities are given in kcal/mol.<sup>b</sup>Entropies are given in cal/(molK).<sup>c</sup>Equilibrium population fractions are denoted by  $x$ .**FIGURE 2** Conformers of N-protonated  $\alpha$ -alanine obtained at the CCSD(T)-F12b/aug-cc-pVDZ level of theory

the results of successful geometry optimizations. Those optimizations that do not converge within 100 steps (default in MOLPRO) or rearranged into N-protonated ones are considered unsuccessful.

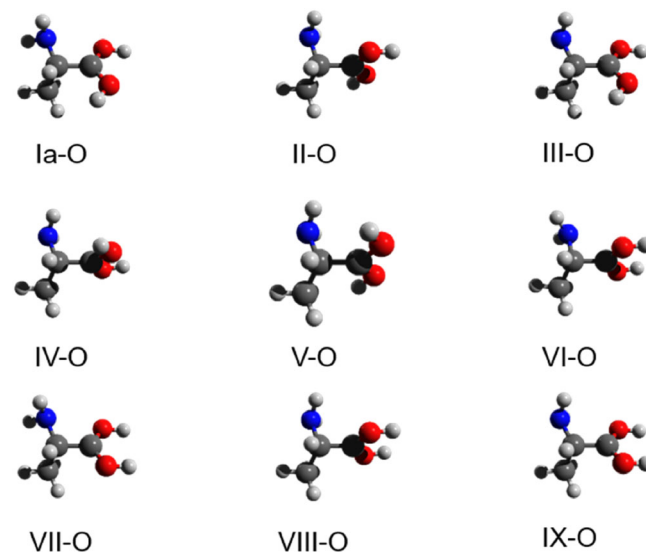
The above systematic conformational search for the N- and O-protonated  $\alpha$ -alanine at the MP2/aug-cc-pVDZ level is followed by geometry optimizations and frequency computations at the CCSD(T)-F12b/aug-cc-pVDZ level of theory. Then, at the CCSD(T)-F12b/aug-cc-pVDZ structures single-point energy computations are performed using both the CCSD(T)-F12a and CCSD(T)-F12b methods<sup>40</sup> with the aug-cc-pVnZ and cc-pVnZ-F12 [ $n = 2(\text{D})$  and 3 (T)] basis sets<sup>41,42</sup> for the conformers of  $\alpha$ -alanine and its protonated species.

The Cartesian coordinates of the benchmark CCSD(T)-F12b/aug-cc-pVDZ structures and the corresponding harmonic vibrational frequencies of the neutral, N-protonated, and O-protonated  $\alpha$ -alanine conformers are given in the Supporting Information.

DFT is also applied to determine the structures of the neutral and protonated  $\alpha$ -alanine conformers utilizing the SOGGA11-X,<sup>43</sup> M06-2X,<sup>44</sup> PBE0,<sup>45</sup> B3LYP,<sup>46</sup> M06,<sup>44</sup> and TPSS<sup>47</sup> functionals with the aug-cc-pVDZ<sup>41</sup> and def2-TZVP<sup>48</sup> basis sets. For these DFT computations, the default settings of MOLPRO are used.

**TABLE 2** Thermodynamic properties of gas-phase N-protonated  $\alpha$ -alanine conformers at the CCSD(T)-F12b/aug-cc-pVTZ//CCSD(T)-F12b/aug-cc-pVDZ level ( $T = 298.15$  K,  $p = 100,000$  Pa)

| Conformer | $\Delta E_{\text{e,rel}}^a$ | $\Delta H_{0,\text{rel}}^a$ | $\Delta H_{\text{rel}}^{\circ a}$ | $\Delta G_{\text{rel}}^{\circ a}$ | $\Delta S^{\circ b}$ | $x^{\circ c}$ |
|-----------|-----------------------------|-----------------------------|-----------------------------------|-----------------------------------|----------------------|---------------|
| Ia-N      | 0.00                        | 0.00                        | 0.00                              | 0.00                              | 77.50                | 0.9987        |
| II-N      | 4.21                        | 4.07                        | 4.16                              | 3.95                              | 78.18                | 0.0013        |
| III-N     | 7.89                        | 7.88                        | 8.35                              | 7.26                              | 81.15                | 0.0000        |

<sup>a</sup>Energy related quantities are given in kcal/mol.<sup>b</sup>Entropies are given in cal/(molK).<sup>c</sup>Equilibrium population fractions are denoted by  $x$ .**FIGURE 3** Conformers of O-protonated  $\alpha$ -alanine obtained at the CCSD(T)-F12b/aug-cc-pVDZ level of theory

All the ab initio and DFT computations are carried out using the MOLPRO<sup>49</sup> program package.

The geometric similarity of two conformers as paired sets of  $n$  spatial points can be characterized by the root-mean-square deviation in the optimal alignment. The numerical details of the determination of the optimal alignment and the permutationally invariant metric of structural similarity are described in the Supporting Information.

## 2.2 | Statistical mechanical gas-phase thermochemistry of protonation

Two of the most important thermodynamic quantities describing a gas-phase proton exchange,



are PA and GB. The PA and GB values of  $\text{B}_{(\text{g})}$  are the negatives of the enthalpy- and Gibbs free energy changes at temperature  $T$  and standard pressure, respectively, that is,

$$PA = -\Delta H_{\text{prot}}^{\circ} \quad (2)$$

$$GB = -\Delta G_{\text{prot}}^{\circ} \quad (3)$$

where the superscript circle denotes that the given thermodynamic quantity is in the standard state. The standard pressure equals to 1 bar, that is, 100,000 Pa, and we use  $T = 298.15$  K as reference temperature. Molar enthalpies and Gibbs free energies of polyatomic molecules can be calculated with an ab initio statistical mechanical approach using the rigid rotor and harmonic oscillator approximations as detailed in the Supporting Information.

According to the classical approximation the gaseous free proton only possesses translational freedom.  $\Delta H_{\text{H}^+}^{\circ}$  can be derived from the equipartition principle and the ideal gas law, whereas the Gibbs energy,  $\Delta G_{\text{H}^+}^{\circ}$ , comes directly from the translational partition function. The enthalpy and Gibbs free energy values of proton at the standard pressure, 100,000 Pa, and 298.15 K are 1.48 kcal/mol and  $-6.28$  kcal/mol, respectively. Fifen et al. calculated these values more accurately by considering quantum chemical effects.<sup>50</sup> In our PA and GB calculations we have instead used these corrected values:  $\Delta H_{\text{H}^+}^{\circ} = 1.47$  kcal/mol and  $\Delta G_{\text{H}^+}^{\circ} = -6.30$  kcal/mol.<sup>50</sup>

The enthalpy- (or Gibbs free energy-) change following a chemical reaction is the difference of the total enthalpies (or Gibbs free energies) of the products and the starting compounds. If  $B_{(g)}$  base and  $BH_{(g)}^+$  conjugate acid exist as a mixture of conformers, the thermodynamic properties of the whole system can be expressed as the corresponding quantities weighted by the equilibrium population fractions as described in detail in the Supporting Information.

### 3 | RESULTS AND DISCUSSION

#### 3.1 | Neutral $\alpha$ -alanine conformers

The 13 conformers of the neutral  $\alpha$ -alanine are shown in Figure 1. The numbering scheme of neutral conformers follows the notation introduced in Ref. [2]. This labeling can be traced back to glycine conformers.<sup>1</sup> In the case of glycine, Ip, Vlp, and VIIp conformers have  $C_s$  symmetry (p stands for planar) therefore any of the two methylene hydrogens can be replaced by a methyl group, the resulting  $\alpha$ -alanines will be chemically equivalent. In contrast, glycines IIIn, IIIIn, IVn, Vn, and VIIIn belong to the point group  $C_1$  ( $n$  denotes the nonexistence of a planar symmetry) meaning that their methylene hydrogens are not equivalent. Replacing one of them with a methyl group results in two different  $\alpha$ -alanine structures, a and b. Depending on the method of optimization, these two initial geometries may result in two different conformers, but not necessarily. Our high-level CCSD(T)-F12b/aug-cc-pVDZ optimizations confirm the 13 different conformers of  $\alpha$ -alanine.

Thermodynamic properties including relative energies, enthalpies, and Gibbs free energies of  $\alpha$ -alanine conformers are collected in Table 1. Neutral  $\alpha$ -alanines can be categorized into low and high-energy conformers depending on their relative energy. There are nine

**TABLE 3** Thermodynamic properties of gas-phase O-protonated  $\alpha$ -alanine conformers at the CCSD(T)-F12b/aug-cc-pVTZ//CCSD(T)-F12b/aug-cc-pVDZ level ( $T = 298.15$  K,  $p = 100,000$  Pa)

| Conformer | $\Delta E_{\text{e,rel}}^a$ | $\Delta H_{0,\text{rel}}^a$ | $\Delta H_{\text{rel}}^a$ | $\Delta G_{\text{rel}}^a$ | $\Delta S^b$ | $x^c$  |
|-----------|-----------------------------|-----------------------------|---------------------------|---------------------------|--------------|--------|
| Ia-O      | 0.00                        | 0.59                        | 0.80                      | 0.33                      | 80.62        | 0.2668 |
| II-O      | 0.11                        | 0.66                        | 0.80                      | 0.56                      | 79.86        | 0.1818 |
| III-O     | 0.40                        | 0.00                        | 0.00                      | 0.00                      | 79.05        | 0.4674 |
| IV-O      | 0.82                        | 1.33                        | 1.54                      | 1.08                      | 80.61        | 0.0757 |
| V-O       | 3.22                        | 3.51                        | 3.78                      | 3.12                      | 81.23        | 0.0024 |
| VI-O      | 3.26                        | 3.31                        | 3.70                      | 2.90                      | 81.73        | 0.0035 |
| VII-O     | 4.06                        | 3.12                        | 2.85                      | 3.27                      | 77.65        | 0.0019 |
| VIII-O    | 4.85                        | 5.00                        | 5.27                      | 4.75                      | 80.80        | 0.0002 |
| IX-O      | 4.91                        | 4.91                        | 5.25                      | 4.36                      | 82.01        | 0.0003 |

<sup>a</sup>Energy related quantities are given in kcal/mol.

<sup>b</sup>Entropies are given in cal/(molK).

<sup>c</sup>Equilibrium population fractions are denoted by  $x$ .

**TABLE 4** Thermodynamic properties of neutral and protonated  $\alpha$ -alanine gases as mixtures of conformers at the CCSD(T)-F12b/aug-cc-pVTZ//CCSD(T)-F12b/aug-cc-pVDZ level of theory ( $T = 298.15$  K,  $p = 100,000$  Pa)

| Conformer mixture | $\Delta H_{\text{av,BH}^+}^{\circ} - \Delta H_{\text{av,B}}^{\circ}$ | $\Delta S_{\text{mix}}^b$ | $\Delta S_{\text{av}}^b$ | $\Delta S_{\text{corr}}^b$ |
|-------------------|--|---------------------------|--------------------------|----------------------------|
| Neutral           |  | 3.45                      | 80.66                    | 84.11                      |
| N-protonated      | $-215.33$  | 0.02                      | 77.50                    | 77.52                      |
| O-protonated      | $-189.16$  | 2.51                      | 79.75                    | 82.26                      |

<sup>a</sup>The difference of average enthalpies are given in kcal/mol.

<sup>b</sup>Entropies are given in cal/(molK).

conformers, I to Vb, with a relative energy of not greater than 2.25 kcal/mol. The equilibrium population fractions of these conformers exceed 1% under standard conditions as also shown in Table 1. Each of the high-energy conformers has *trans*-carboxylic groups (*trans* arrangement of the carbonyl O and hydroxyl H in  $O=C-O-H$ ) and all *cis*-carboxylic group possessing conformers belong to the low-energy ones, except IIa and IIb as these low-energy conformers have a *trans*-carboxylic group. Their low energy may be due to an extra stabilizing interaction, hydrogen bond, between the amino nitrogen and the carboxylic hydrogen. ZPE effects on the relative energies are usually around 0.2–0.3 kcal/mol and the thermal enthalpy corrections are often small (0.01–0.02 kcal/mol), the largest thermal effect of 0.18 kcal/mol is found for IIb. Entropy effects are somewhat larger as the  $\Delta H_{\text{rel}}^{\circ}$  and  $\Delta G_{\text{rel}}^{\circ}$  values usually differ by 0.1–0.2 kcal/mol and the largest difference of 0.45 kcal/mol is again found for IIb.

#### 3.2 | N-protonated $\alpha$ -alanine conformers

In our recent high-level ab initio study on the protonated glycine, we found 3 N-protonated conformers, all with  $C_s$  symmetry.<sup>36</sup>

**TABLE 5** CCSD(T)-F12b/aug-cc-pVTZ//CCSD(T)-F12b/aug-cc-pVDZ proton affinity (PA) and gas-phase basicity (GB) of  $\alpha$ -alanine at different protonation sites

| Temperature/<br>pressure <sup>a</sup> | N-protonation   |                 | O-protonation   |                 |
|---------------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                       | PA <sup>b</sup> | GB <sup>b</sup> | PA <sup>b</sup> | GB <sup>b</sup> |
| 298.15/100,000                        | 216.80          | 207.07(208.09)  | 190.63          | 182.31(182.59)  |
| 298.15/101,325                        | 216.80          | 207.08(208.10)  | 190.63          | 182.32(182.60)  |
| 0                                     | 214.47          |                 | 189.04          |                 |

<sup>a</sup>The temperatures and pressures are given in K and Pa, respectively.<sup>b</sup>PA and GB values are given in kcal/mol. The GB values in parentheses are calculated without the correction of  $\Delta S_{\text{mix}}^{\circ}$ .**TABLE 6** Comparison of the experimental and the present theoretical proton affinity (PA) and gas-phase basicity (GB) of  $\alpha$ -alanine (in kcal/mol at  $T = 298.15$  K,  $p = 100,000$  Pa)

| PA                           | GB                          | References                           | Comments <sup>a</sup>                 |
|------------------------------|-----------------------------|--------------------------------------|---------------------------------------|
| <b>Theory</b>                |                             |                                      |                                       |
| 216.80                       | 207.07(208.09) <sup>b</sup> | This work                            | See Table 5                           |
| <b>Experiment</b>            |                             |                                      |                                       |
| 212.2 $\pm$ 1.5 <sup>c</sup> |                             | Meot-Ner et al. (1979) <sup>51</sup> | Pulsed ionization high-pressure MS    |
| 215.8                        | 207.4                       | Locke et al. (1983) <sup>52</sup>    | Pulsed ICR MS                         |
| 214.8                        | 206.6                       | Lias et al. (1984) <sup>53</sup>     | Critical evaluation                   |
| 222.1 $\pm$ 2.9              | 212.3 $\pm$ 2.5             | Gorman et al. (1992) <sup>22</sup>   | $T = 350$ K                           |
| 213.6 $\pm$ 0.1              |                             | Li et al. (1993) <sup>54</sup>       | Hybrid tandem MS, Lias scale          |
| 219.2 $\pm$ 0.3              |                             | Li et al. (1993) <sup>54</sup>       | Hybrid tandem MS, Meot-Ner scale      |
| 218.1                        | 210.4 $\pm$ 3               | Cassady et al. (1995) <sup>23</sup>  | Fourier transform ICR MS              |
| 214 $\pm$ 0.05               |                             | Afonso et al. (2000) <sup>27</sup>   | Electrospray ionization-ion trap MS   |
| 215.6 $\pm$ 1                | 207.7                       | Hahn et al. (2003) <sup>55</sup>     | EKM, GB based on Table 1 of Ref. [55] |

<sup>a</sup>MS, mass spectrometry; ICR, ion cyclotron resonance; EKM, extended kinetic method.<sup>b</sup>The GB value in parenthesis is calculated without the correction of  $\Delta S_{\text{mix}}^{\circ}$ .<sup>c</sup>According to the footnote of Table 1 of Ref. [51], the PA of the reference base ( $\text{NH}_3$ ) might be underestimated by 5 kcal/mol; thus, the PA of  $\alpha$ -alanine could be around 217 kcal/mol.

Thus, one may also expect 3 N-protonated conformers for  $\alpha$ -alanine. During our systematic search we have indeed found 3 N-protonated  $\alpha$ -alanine conformers at the MP2/aug-cc-pVDZ level of theory, which have also been confirmed at the CCSD(T)-F12b/aug-cc-pVDZ level as shown in Figure 2. These N-protonated  $\alpha$ -alanine structures, denoted as Ia-N, II-N, and III-N, are similar to the Ip<sub>N</sub> (1m), Ilp<sub>N</sub> (2m), and Illp<sub>N</sub> (3m) protonated glycines, respectively, reported in Ref. [36, 37].

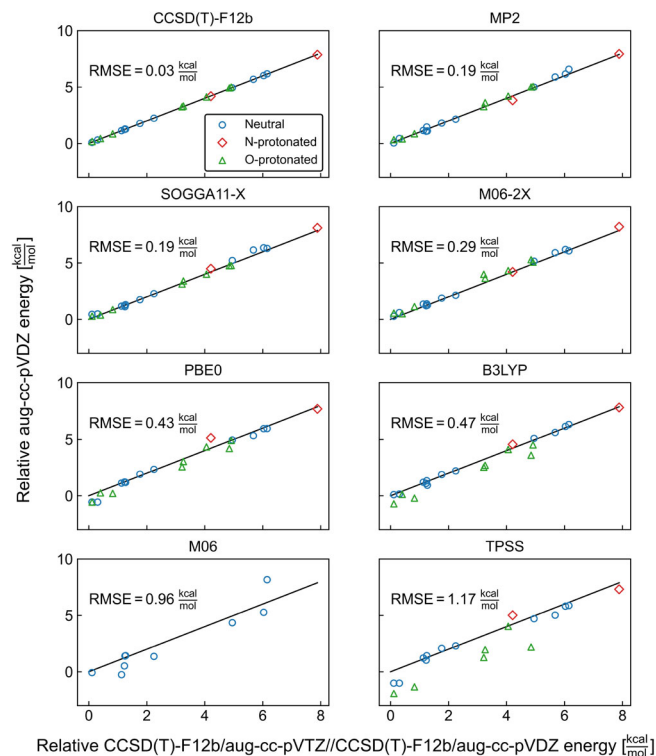
Table 2 shows the thermodynamic properties of the N-protonated  $\alpha$ -alanine conformers. From the three N-protonated conformers only one, Ia-N has significant population fraction under standard conditions. The equilibrium energies of the II-N and III-N conformers are 4.21 and 7.89 kcal/mol, respectively, relative to Ia-N. The temperature effects are significant, especially in the case of III-N. In accordance with the relative energies of the neutral ones, the highest-energy N-protonated structure has a *trans*-carboxylic group, that is, the O—H and C=O bonds are in *trans* positions in O=C—O—H. The main structural difference between Ia-N and the lower high-energy conformer II-N is that in the former case the carbonyl group of the *cis*-carboxylic group interacts with the ammonium hydrogen. In the latter case, the interaction is between the ammonium hydrogen and the hydroxyl oxygen.

### 3.3 | O-protonated $\alpha$ -alanine conformers

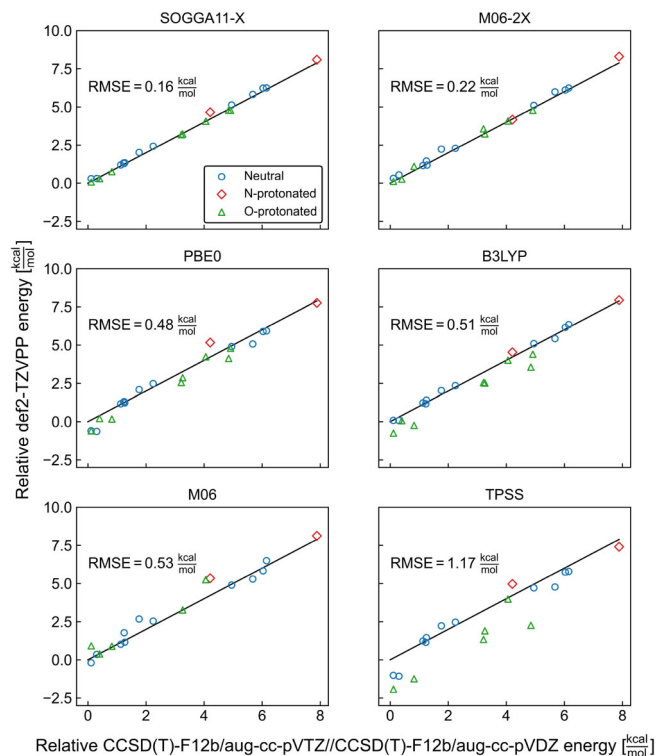
We have found nine O-protonated  $\alpha$ -alanine conformers as shown in Figure 3. According to our recent benchmark study<sup>36</sup> there are eight O-protonated glycine conformers, namely In<sub>O</sub> (4m), Ilp<sub>O</sub> (5m), Illn<sub>O</sub> (6m), IVn<sub>O</sub> (7m), Vn<sub>O</sub>, Vlp<sub>O</sub> (8m), Vlln<sub>O</sub>, and Vllln<sub>O</sub>, where roman numbers reflect the energy order, n/p denotes C<sub>1</sub>/C<sub>s</sub> symmetry, and in parentheses the five conformers reported in the old work of Zhang and Chung-Phillips<sup>37</sup> are shown. From the C<sub>s</sub> or nearly C<sub>s</sub> Ilp<sub>O</sub> (5m), IVn<sub>O</sub> (7m), and Vlp<sub>O</sub> (8m) protonated glycines, the III-O, VII-O, and IX-O structures can be derived by methyl substitutions, respectively. II-O and IV-O are both can be traced back to the Illn<sub>O</sub> (6m) asymmetric protonated glycine conformer. Ia-O can be identified as one of the two methyl substituted In<sub>O</sub> (4m) geometries. The other conformer which may be derived from In<sub>O</sub> (4m) does not exist at our highest-level geometry optimization. Finally, V-O, VI-O, and VIII-O can be paired with the Vlln<sub>O</sub>, Vn<sub>O</sub>, and Vllln<sub>O</sub> O-protonated glycine structures, respectively.

Low-relative energy O-protonated  $\alpha$ -alanine conformers (Ia-O–IV-O) contain a *cis-trans* C(OH)<sub>2</sub><sup>+</sup> group and the four highest energy conformers have *cis-cis* (considering the O—C—O—H atoms)





**FIGURE 4** Correlation between relative electronic energies of neutral, N-protonated, and O-protonated  $\alpha$ -alanine conformers computed at different levels of theory and the benchmark relative electronic energies. I, Ia-N, and Ia-O conformers with zero reference values are not included



**FIGURE 5** Correlation between relative electronic energies of neutral, N-protonated, and O-protonated  $\alpha$ -alanine conformers computed with different DFTs using the def2-TZVPP basis set and the benchmark relative electronic energies. I, Ia-N, and Ia-O conformers with zero reference values are not included

protonated carboxylic group. Only one conformer, V-O, possesses a *trans-trans*  $C(OH)_2^+$  group, whose relative energy falls between the energies of the *cis-trans* and *cis-cis* geometries.

As Table 3 shows the nine O-protonated conformers are in a 5 kcal/mol energy range and the order of the conformers changes upon applying ZPE and thermal corrections. Ia-O is the lowest energy conformer classically, whereas III-O has the deepest energy adiabatically or at standard temperature. In some cases, the ZPE, thermal enthalpy, and, especially, the entropy corrections are significant, for example, around 0.5–0.9 kcal/mol as also shown in Table 3.

### 3.4 | Benchmark proton affinities and gas-phase basicities of $\alpha$ -alanine

Our best predictions for the thermodynamic data of neutral, N-, and O-protonated  $\alpha$ -alanine mixtures of conformers are given in Table 4. As seen, protonation is a highly exothermic process and the average standard enthalpy of the O-protonated conformers is above the N-protonated value by 26.17 kcal/mol. As the highest-energy III-N conformer is above Ia-N by 8.35 kcal/mol, it is clear that there is no energy overlap between N- and O-protonated  $\alpha$ -alanine conformers. Utilizing the enthalpy and entropy data shown in Table 4 and

the  $\Delta H_{H^+}^\circ = 1.47$  kcal/mol and  $\Delta G_{H^+}^\circ = -6.30$  kcal/mol values, the benchmark PA and GB values of  $\alpha$ -alanine, given in Table 5, can be obtained. For example, the PA and GB for N-protonation at 298.15 K can be calculated as  $215.33 + 1.47 = 216.80$  kcal/mol and  $215.33 - 298.15 \times (0.08411 - 0.07752) - 6.30 = 207.07$  kcal/mol, respectively. As seen, the substantial difference of Gibbs free energy and enthalpy of the proton, that is,  $-7.76$  kcal/mol, and the also significant entropy correction of  $-1.96$  kcal/mol (N-protonation) make the GB value smaller than the corresponding PA. At 298.15 K the N-protonation PA is larger by 26.17 kcal/mol than the PA for O-protonation (see this value also above), whereas at 0 K the PA difference is 25.43 kcal/mol, which corresponds to the adiabatic (ZPE-corrected) energy of Ia-O relative to Ia-N. The standard GB for N-protonation is above the O-protonation value by 24.76 kcal/mol showing a 1.41 kcal/mol entropy-effect difference between N- and O-protonation. The computed standard PA and GB values of 216.80 and 207.07 kcal/mol for N-protonation can be compared with the experimental data<sup>22,23,27,51–55</sup> which vary in the wide ranges of 212–222 and 207–212 kcal/mol, respectively, as shown in Table 6. As seen, the theoretical predictions are within these intervals of the measured data. Furthermore, it is important to note that some of experimental data have large error bars of around 2–3 kcal/mol, whereas the uncertainty of the present computed values is expected to be significantly less, around 1 kcal/mol, as

**TABLE 7** Relative electronic energies (kcal/mol) of the neutral, N-protonated, and O-protonated  $\alpha$ -alanine conformers (compared to I, Ia-N, and Ia-O, respectively) computed at different levels of theory using the aug-cc-pVDZ basis set

| Conformer | CCSD(T)-F12b | MP2  | SOGGA11-X | M06-2X | PBE0  | B3LYP | M06 <sup>a</sup> | TPSS  |
|-----------|--------------|------|-----------|--------|-------|-------|------------------|-------|
| I         | 0.00         | 0.00 | 0.00      | 0.00   | 0.00  | 0.00  | 0.00             | 0.00  |
| Ila       | 0.31         | 0.43 | 0.48      | 0.60   | −0.56 | 0.15  |                  | −1.01 |
| Ilb       | 0.09         | 0.04 | 0.44      | 0.27   | −0.56 | 0.10  | −0.07            | −1.01 |
| IIla      | 1.26         | 1.10 | 1.30      | 1.24   | 1.18  | 0.93  | 1.43             |       |
| IIlb      | 1.23         | 1.08 | 1.23      | 1.21   | 1.21  | 1.10  | 0.52             | 1.03  |
| IVa       | 1.13         | 1.15 | 1.17      | 1.36   | 1.12  | 1.19  | −0.26            | 1.22  |
| IVb       | 1.28         | 1.46 | 1.12      | 1.38   | 1.21  | 1.33  | 1.40             | 1.42  |
| Va        | 2.23         | 2.14 | 2.28      | 2.14   | 2.33  | 2.20  | 1.36             | 2.29  |
| Vb        | 1.77         | 1.81 | 1.75      | 1.89   | 1.91  | 1.88  |                  | 2.08  |
| VI        | 4.93         | 4.99 | 5.23      | 5.17   | 4.95  | 5.09  | 4.35             | 4.71  |
| VII       | 5.69         | 5.89 | 6.16      | 5.92   | 5.33  | 5.61  |                  | 5.02  |
| VIIIa     | 6.02         | 6.16 | 6.36      | 6.20   | 5.95  | 6.15  | 5.27             | 5.81  |
| VIIIb     | 6.18         | 6.58 | 6.30      | 6.09   | 5.96  | 6.32  | 8.16             | 5.87  |
| Ia-N      | 0.00         | 0.00 | 0.00      | 0.00   | 0.00  | 0.00  |                  | 0.00  |
| II-N      | 4.19         | 3.82 | 4.49      | 4.21   | 5.13  | 4.56  |                  | 5.01  |
| III-N     | 7.87         | 7.93 | 8.12      | 8.21   | 7.70  | 7.83  |                  | 7.31  |
| Ia-O      | 0.00         | 0.00 | 0.00      | 0.00   | 0.00  | 0.00  |                  | 0.00  |
| II-O      | 0.17         | 0.33 | 0.28      | 0.55   | −0.57 | −0.72 |                  | −1.93 |
| III-O     | 0.43         | 0.40 | 0.38      | 0.50   | 0.25  | 0.12  |                  |       |
| IV-O      | 0.84         | 0.85 | 0.86      | 1.13   | 0.21  | −0.21 |                  | −1.34 |
| V-O       | 3.25         | 3.26 | 3.14      | 3.99   | 2.56  | 2.53  |                  | 1.27  |
| VI-O      | 3.31         | 3.61 | 3.41      | 3.65   | 3.03  | 2.69  |                  | 1.96  |
| VII-O     | 4.12         | 4.19 | 4.01      | 4.32   | 4.33  | 4.09  |                  | 4.02  |
| VIII-O    | 4.92         | 5.01 | 4.76      | 5.30   | 4.19  | 3.59  |                  | 2.19  |
| IX-O      | 5.00         | 5.05 | 4.77      | 5.07   | 4.90  | 4.50  |                  |       |

<sup>a</sup>For the protonated conformers (which are comparable to the coupled-cluster counterparts) only II-N, VI-O, and VII-O are obtained. Due to the missing Ia-N and Ia-O structures, relative energies are not given.

discussed in the next section. Our computed PA/GB{GB without  $\Delta S_{\text{mix}}^{\circ}$ } values (216.80/207.07{208.09}) have the best agreement with those of Locke and McIver (215.8/207.4)<sup>52</sup> and Hahn and Wesdemiotis (215.6/207.7),<sup>55</sup> all given in kcal/mol. Finally, it is interesting to compare the PA(GB) values of  $\alpha$ -alanine, that are 216.80(207.07) and 190.63(182.31) kcal/mol for N- and O-protonation at 298.15 K, with the corresponding recent theoretical values of glycine, 212.43 (204.75) and 187.64(180.21) kcal/mol,<sup>36</sup> respectively. The slight increase in the PA and GB of  $\alpha$ -alanine relative to the corresponding glycine values is due to the weak electron-donating character of the methyl group present in alanine.

### 3.5 | Assessment of the accuracy of the ab initio and DFT results

The accuracy of the MP2 method and various DFT functionals for the relative energies of the neutral, N- and O-protonated  $\alpha$ -alanine

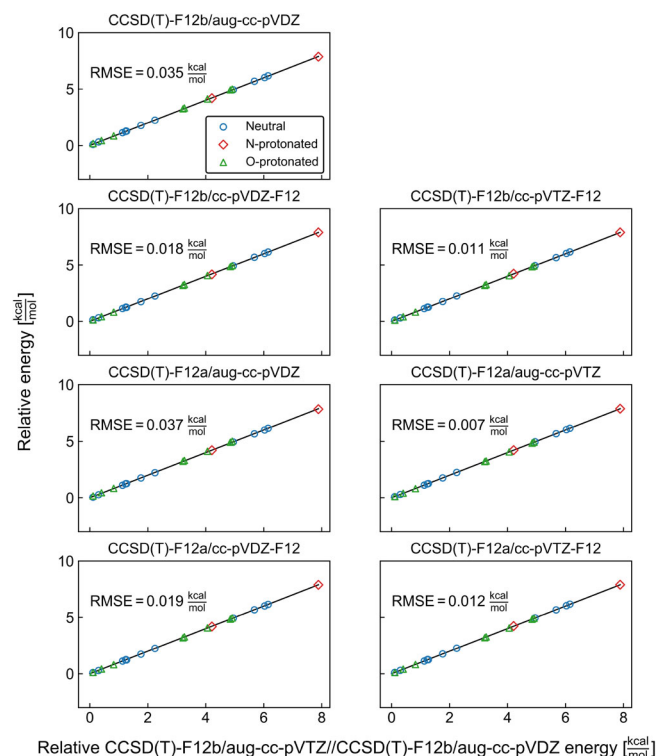
conformers with respect to the benchmark CCSD(T)-F12b/aug-cc-pVTZ//CCSD(T)-F12b/aug-cc-pVDZ results are shown in Figures 4 and 5. The corresponding numerical data are given in Table 7, Tables 1–3, and Table S1. Figure 4 shows that the CCSD(T)-F12b method with the aug-cc-pVDZ and aug-cc-pVTZ basis sets gives the same relative energies with a root-mean-square error (RMSE) of only 0.03 kcal/mol, showing the excellent basis-set convergence of the explicitly-correlated CCSD(T)-F12b method and confirming the accuracy of the final classical relative energies. The MP2 method also performs remarkably well, correlating with the benchmark data with an RMSE of 0.19 kcal/mol. The DFT methods provide larger errors with different magnitudes depending on the choice of the functionals and basis sets. The SOGGA11-X, M06-2X, PBE0, and B3LYP functionals with the aug-cc-pVDZ(def2-TZVPP) basis sets perform quite well, with RMSE values of 0.19(0.16), 0.29(0.22), 0.43(0.48), and 0.47(0.51) kcal/mol, respectively, as shown in Figures 5. The accuracy of the M06 and TPSS functionals is found to be the worst, featuring significant RMSEs of 0.96(0.53) and 1.17(1.17) kcal/mol, in order.

As the above data show, the aug-cc-pVDZ and def2-TZVPP basis sets give similar accuracy, except for M06, where significant improvement is found with the use of the latter basis. Furthermore, as Table 7 shows, the IIa, Vb, and VII conformers of  $\alpha$ -alanine cannot be obtained by M06/aug-cc-pVDZ and the search for protonated  $\alpha$ -alanine conformers has only been successful for II-N, VI-O, and VII-O with this functional. If we use the def2-TZVPP basis, M06 provides more conformers and only IIIb, V-O, VIII-O, and IX-O are missing, as shown in Table S1. With TPSS there are also a few missing conformers, namely IIIa, III-O, and IX-O with both basis sets. The other DFT functionals

give the same conformers as the ab initio methods if the same aug-cc-pVDZ basis set is used, only the energy order of the close-lying conformers changes at a few places as Table 7 shows. Using the def2-TZVPP basis there are missing conformers with M06-2X (IIIb and VIII-O) and B3LYP (IIIa) as seen in Table S1. We should also note that in some cases DFT finds new protonated conformers such as Ib-N with SOGGA11-X/aug-cc-pVDZ and M06-2X/aug-cc-pVDZ and Ib-O with SOGGA11-X and M06-2X in the case of both basis sets or M06 and TPSS with aug-cc-pVDZ (Tables S2 and S3).

We have also tested the performance of the F12a and F12b variants of the CCSD(T)-F12 method with different correlation-consistent basis sets. As Figure 6 shows the aug-cc-pVDZ and cc-pVDZ-F12 basis sets provide relative conformer energies with RMSE values of 0.03–0.04 and 0.02 kcal/mol, respectively, without any significant dependence on the choice between F12a and F12b. Using triple-zeta basis sets, the relative energies agree within about 0.01 kcal/mol for any combination of the F12a and F12b methods and the aug-cc-pVTZ and cc-pVTZ-F12 basis sets as also shown in Figure 6.

Proton affinities obtained with different ab initio and DFT methods are collected in Tables 8–10. By comparing the CCSD(T)-F12b/aug-cc-pVDZ PA values with the corresponding benchmark data shown in Table 5, it seems that the PA results are basis-set converged within 0.1 kcal/mol as the aug-cc-pVDZ and aug-cc-pVTZ data differ by only 0.03 and 0.07 kcal/mol for N- and O-protonation,



**FIGURE 6** Correlation between relative electronic energies of neutral, N-protonated, and O-protonated  $\alpha$ -alanine conformers computed with different variants of the CCSD(T)-F12 method and the correlation-consistent basis sets using CCSD(T)-F12b/aug-cc-pVDZ geometries. I, Ia-N, and Ia-O conformers with zero reference values are not included

**TABLE 10** Proton affinities (kcal/mol) computed with different variants of the CCSD(T)-F12 method and the correlation-consistent basis sets using CCSD(T)-F12b/aug-cc-pVDZ geometries and vibrational energies ( $T = 298.15$  K,  $p = 100,000$  Pa)

|              |             | N-protonation | O-protonation |
|--------------|-------------|---------------|---------------|
| CCSD(T)-F12a | aug-cc-pVDZ | 216.66        | 190.54        |
|              | aug-cc-pVTZ | 216.67        | 190.47        |
|              | cc-pVDZ-F12 | 216.94        | 190.63        |
|              | cc-pVTZ-F12 | 216.72        | 190.47        |
| CCSD(T)-F12b | aug-cc-pVDZ | 216.83        | 190.70        |
|              | aug-cc-pVTZ | 216.80        | 190.63        |
|              | cc-pVDZ-F12 | 217.11        | 190.83        |
|              | cc-pVTZ-F12 | 216.80        | 190.57        |

**TABLE 8** Proton affinities (kcal/mol) computed at different levels of theory using the aug-cc-pVDZ basis set ( $T = 298.15$  K,  $p = 100,000$  Pa)

|               | CCSD(T)-F12b | MP2    | SOGGA11-X | M06-2X | PBE0   | B3LYP  | M06    | TPSS   |
|---------------|--------------|--------|-----------|--------|--------|--------|--------|--------|
| N-protonation | 216.83       | 214.22 | 216.31    | 214.15 | 217.18 | 215.73 | 205.95 | 217.92 |
| O-protonation | 190.70       | 186.51 | 191.83    | 189.95 | 192.72 | 191.68 | 186.35 | 193.63 |

**TABLE 9** Proton affinities (kcal/mol) computed with different DFTs using the def2-TZVPP basis set ( $T = 298.15$  K,  $p = 100,000$  Pa)

|               | SOGGA11-X | M06-2X | PBE0   | B3LYP  | M06    | TPSS   |
|---------------|-----------|--------|--------|--------|--------|--------|
| N-protonation | 218.61    | 214.50 | 218.68 | 217.37 | 216.56 | 219.59 |
| O-protonation | 194.35    | 190.96 | 194.44 | 193.31 | 193.08 | 195.36 |



respectively. The MP2 method does not provide PA values with chemical accuracy, since MP2 significantly underestimates the CCSD(T)-F12b PA results by 2.61 and 4.19 kcal/mol in the case of N- and O-protonation, respectively. The accuracy of the DFT functionals with the aug-cc-pVDZ basis is found to be around 1–3 kcal/mol for the PA values, except in the case of M06 where about 11 kcal/mol (N-protonation) and 4 kcal/mol (O-protonation) errors are obtained (see Table 8), due to the fact that the lowest-energy protonated conformers are missing. If the def2-TZVPP basis is used, the errors of the functionals other than M06 are usually larger being in the 1–5 kcal/mol range, whereas for M06 the tremendous deviations significantly decrease (see Table 9), because the missing lowest-energy conformers can be found at the M06/def2-TZVPP level. The comparison of the PA values obtained with various coupled-cluster levels is shown in Table 10. As seen, the F12a and F12b methods provide the same results within 0.1–0.2 kcal/mol and the agreement is better with triple-zeta basis sets. The difference between the double- and triple-zeta PA results is slightly less in the case of the CCSD(T)-F12a method as somewhat expected. However, unexpectedly, the aug-cc-pVnZ basis sets show better convergence than cc-pVnZ-F12, as the  $n = D$  and  $T$  PA values agree within about 0.1 and 0.2–0.3 kcal/mol, respectively.

## 4 | SUMMARY AND CONCLUSIONS

We have performed high-level explicitly-correlated CCSD(T)-F12b computations for the 13 known conformers of  $\alpha$ -alanine and carried out a systematic conformational search for the N- and O-protonated  $\alpha$ -alanine revealing three and nine conformers, respectively. The 13  $\alpha$ -alanine conformers can be derived from the 3  $C_s$  and 5  $C_1$  conformers of glycine as  $3 + 2 \times 5$ . The 3 N-protonated  $\alpha$ -alanine structures correspond to the 3  $C_s$  N-protonated glycine conformers. In the case of O-protonation, the protonated  $\alpha$ -alanine conformers are also similar to those of glycine; though in the case of glycine the number of conformers is only eight instead of nine. The 13 neutral, the 3 N-protonated, and the 9 O-protonated  $\alpha$ -alanine conformers span about 6, 8, and 5 kcal/mol energy ranges, respectively, without any overlap, as the energy difference between the Ia-N and Ia-O conformers is about 26 kcal/mol.

Benchmark PA and GB values of  $\alpha$ -alanine are obtained within the range of the scattered experimental data and may have smaller uncertainties than the measured values. As expected, the temperature effects between the 0 and 298.15 K PA values are around 1–2 kcal/mol, mostly coming from the translational enthalpy of the proton (1.47 kcal/mol). The GB values are significantly below the PA ones, mostly because of the Gibbs free energy of the proton (−6.30 kcal/mol). The vibrational and rotational thermal effects are small, but not negligible, especially for GB. The CCSD(T)-F12b PA values are basis-set converged within 0.1 kcal/mol. MP2 provides good accuracy for the relative energies of the conformers with an uncertainty of about 0.1–0.2 kcal/mol, whereas the MP2 PA values are substantially smaller than the CCSD(T)-F12b data by 2–4 kcal/mol. The average performance of the DFT functionals

investigated in the present study for the relative energies of the conformers is as follows SOGGA11-X (0.19/0.16), M06-2X (0.29/0.22), PBE0 (0.43/0.48), B3LYP (0.47/0.51), M06 (0.96/0.53), and TPSS (1.17/1.17) showing their RMS errors (kcal/mol) with the aug-cc-pVDZ/def2-TZVPP basis sets in parentheses. For the PA values these functionals give 1–3/1–5 kcal/mol errors, except M06 with aug-cc-pVDZ which has an order of magnitude larger uncertainty due to the missing lowest-energy protonated conformers.

To assess the final accuracy of the present benchmark results one should consider the followings: (a) Basis-set convergence, (b) Post-CCSD(T) correlation, (c) Core correlation, (d) Relativistic effects, and (e) Vibrational anharmonicity. (a) is better than 0.1 kcal/mol based on the present PA results; (b), (c), and (d) are likely to be small as their cumulative effect was found to be +0.09/−0.12 kcal/mol for N-/O-protonation of glycine<sup>36</sup>; and (e) is expected to be less than 0.1 kcal/mol for the ZPE corrections,<sup>13,18</sup> but the uncertainty of the low frequencies may affect significantly the thermal corrections, especially in the case of the entropy effects, causing a few tenths of kcal/mol and around 1 kcal/mol uncertainty estimates for the final PA and GB values, respectively. Future work may consider second-order vibrational perturbation theory and/or hindered rotor analysis for the low frequency, large-amplitude modes to improve the accuracy of the present results. Further experiments would also be necessary, because the present PA computations have reached a level of accuracy, which is better and/or more certain than that of the available experiments.

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## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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