# Theoretical calculations of glycine and alanine gas-phase acidities

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# Theoretical Calculations of Glycine and Alanine Gas-phase Acidities

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The gas-phase acidities of glycine and alanine were determined by using a variety of high level theoretical methods to establish which of these would give the best results with accessible computational efforts. MP2, MP4, QCISD, G2 ab initio procedures, hybrid Becke3-LYP (B3LYP) and gradient corrected Becke–Perdew (BP) and Perdew–Wang and Perdew (PWP) nonlocal density functionals were used for the calculations. A maximum deviation of approximately 13 and 18 kJ/mol from experimental data was observed for the computed $\Delta H_{acid}$ and $\Delta G_{acid}$ values, respectively. The best result was obtained at G2 level, but comparable reliability was reached when the considerably less time consuming B3LYP, BP, and PWP density functional approaches were employed. (J Am Soc Mass Spectrom 1999, 10, 318–322) © 1999 American Society for Mass Spectrometry

The knowledge of the gas-phase acidity of a molecule is of fundamental importance for the elucidation and interpretation of its reactivity. This is the reason for the growing interest in measuring and predicting gas-phase acidities both with experimental techniques and theoretical methods. Experimentally, these thermochemical data can be obtained by traditional equilibrium or bracketing determinations [1] or by the kinetic [2, 3] method, which also allows measurement for nonvolatile systems. From a theoretical point of view, gas-phase acidities were computed for a series of small organic and inorganic molecules employing Gaussian 2 (G2) [4–7], density functional (DF) [8, 9] and semiempirical PM3 [10] methods. For different simple acids G2 results [4–7] fall within a target accuracy of 8–13 kJ/mol. Recently, Merrill and Kass [8] calculated the gas-phase acidity of 35 acids by using seven different exchange-correlation density functionals. Their study shows that the use of a Becke3-PW91 hybrid functional can give competitive reliability of the results with respect to the G2 ab initio procedure, but it requires less computational effort. This last fact encourages the DF study of larger systems with chemical and biological significance such as amino acids.

Gas-phase acidities of the naturally occurring amino acids were determined by using the kinetic method with collision-induced dissociation in a MIKE experiment [3]. In addition, Locke and McIver [11] determined the acidity of glycine, alanine, and sarcosine via equilibrium measurements in an ion cyclotron resonance mass spectrometer, and Bowie and co-workers [12] studied the mechanisms of the collision-induced fragmentations of deprotonated $\alpha$-amino acids.

As far as we know, only an HF/6-31 + G* [3] theoretical study of the gas-phase acidities of glycine, alanine, serine, and cisteine have been performed. The values of acidity are overestimated by approximatively 42 kJ/mol with respect to experimental measurements.

As a part of a more systematic investigation of amino-acid properties, we wish to prove the reliability of some common theoretical methods to reproduce the gas-phase acidities of alanine and glycine. The choice for these two, not so large molecules was dictated by the lack of high level theoretical studies in this field, and by the need to establish whether it is feasible to extend the calculations to other amino acids. On the other hand, also for these simple systems, the determination of the most stable neutral molecular conformation, which represents the starting point to evaluate the gas-phase acidity, together with the vibrational analysis, still requires many calculations even with powerful workstations.

## Theory

The methods that we chose for our calculations fall under the Hartree–Fock and density functional theories. In particular, the MP2, MP4, QCISD, and G2 ab initio procedures, the hybrid Becke3-LYP, and gradient-corrected Becke–Perdew and Perdew–Wang and Perdew

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**Table 1.** Geometrical parameters of glycine computed at different levels of theory. Distances are in Å and angles in degrees

| Parameter | BP | PWP | B3LYP | MP2 | EXP[a] |
|---|---|---|---|---|---|
| C–C | 1.549 | 1.528 | 1.522 | 1.519 | 1.526 |
| C═O | 1.219 | 1.221 | 1.204 | 1.209 | 1.205 |
| C–O | 1.353 | 1.372 | 1.356 | 1.356 | 1.355 |
| C–N | 1.487 | 1.468 | 1.451 | 1.447 | 1.467 |
| ⟨N–H⟩ | 1.021 | 1.024 | 1.012 | 1.014 | / |
| O–H | 1.007 | 0.984 | 0.968 | 0.968 | / |
| ⟨C–H⟩ | 1.076 | 1.098 | 1.091 | 1.094 | / |
| O–C–O | 123.7 | 122.0 | 122.8 | 123.4 | 123.3 |
| C–C═O | 123.0 | 125.0 | 125.7 | 125.7 | 125.1 |
| C–C–O | 113.3 | 113.0 | 111.5 | 110.9 | 111.6 |
| N–C–C | 109.2 | 115.1 | 115.5 | 115.6 | 112.1 |
| ⟨H–C–C⟩ | 106.5 | 109.0 | 107.7 | 107.4 | / |
| ⟨H–N–C⟩ | 111.3 | 109.3 | 109.9 | 110.2 | / |
| C–O–H | 102.8 | 106.3 | 107.1 | 106.6 | / |

[a]From [31].

non-local-density functionals were employed. All calculations were carried out using the GAUSSIAN 94 [13] and the deMon [14] codes. Full geometry optimization and vibrational analysis were performed using

(i) the gradient-corrected Becke [15] and Perdew [16] (BP) and Perdew and Wang [17] and Perdew [16] (PWP) exchange-correlation potentials;

(ii) the hybrid Becke3-LYP (B3LYP) [18, 19] functional (the triple-zeta basis set with diffusion functions (TZ+) was considered in the case of BP and PWP computations [20] whereas the internal 6-311 + G(*d*,*p*) basis set was employed for the B3LYP ones);

(iii) the Hartree-Fock (HF/6-31G(*d*)) method.

The HF harmonic frequencies were scaled by a factor of 0.893. No scaling factor was used in all other computations.

Only geometry optimization was done at Moller–Plesset second order perturbation [21] (MP2/6-31G(*d*)) level.

Single-point computations on MP2/6-31G(*d*) optimized geometry were carried out with Moller–Plesset fourth order perturbation [21] (MP4), QCISD(T) [22] (by using the different basis sets reported in Tables 3 and 4), and (G2) [23] procedures.

The gas-phase acidity of AH (proton affinity of A−) was obtained as a function of the Gibbs free energy, $\Delta G_{\mathrm{acid},T} = \Delta H_{\mathrm{acid},\ T} - T\Delta S_T$, for the deprotonation reaction:

$$\mathrm{AH} \rightarrow \mathrm{A}^- + \mathrm{H}^+ \tag{1}$$

$\Delta H_{\mathrm{acid},T}$ can be obtained as

$$\Delta H_{\mathrm{acid},T} = \Delta E_{\mathrm{eq}} + \Delta(\mathrm{PV}) + \Delta(\mathrm{ZPE}) + \Delta E_T^{\mathrm{v}} + \Delta_T^{\mathrm{r}} + \Delta E_T^{\mathrm{t}} \tag{2}$$

In our calculations the following approximated expression was used:

$$\Delta H_{\mathrm{acid},298} = \Delta E_{\mathrm{el}} + \mathrm{RT} + \Delta(\mathrm{ZPE}) + \frac{3}{2}\mathrm{RT} + \Delta\left(\sum_i \frac{h\nu_i \exp(-h\nu_i/kT)}{1 - \exp(-h\nu_i/kT)}\right) \tag{3}$$

where $\Delta E_{\mathrm{el}}$ is the variation in internal energy that arises directly from the computations; RT represents the Δ(PV) term necessary to convert internal energy in enthalpy if reagents and products can be considered as ideal gases (this assumption is reasonable for the pressures normally used in the measurements of gas-phase acidities); Δ(ZPE) is the variation in zero-point vibration energies derived by computed harmonic frequencies. Vibrational enthalpy correction is evaluated through the last term of eq 3. The corrections due to translation and rotation ($\Delta E_T^t$, $\Delta E_T^r$) can be treated classically, using the equipartition theorem. Thus, considering that in the final state, we have two species present ($A^-$ and $H^+$) and one (AH) in the initial state, and also that the proton has only translational degrees of freedom, we may write

$$\Delta E_T^t = \frac{3}{2}\mathrm{RT}, \qquad \Delta E_T^r = 0 \tag{4}$$

The entropic contribution to the $\Delta G_{\mathrm{acid},T}$ was calculated as

$$-T\Delta S_T = -T[\mathrm{S(AH)} - S(\mathrm{A}^-) - S(\mathrm{H}^+)] \tag{5}$$

The $TS$(AH) and $TS(A^-)$ terms were obtained from thermochemical calculations by using the theoretical harmonic frequencies at the equilibrium geometries. The value of 32.5 kJ/mol [24] for the $TS(H^+)$ term, at 298 K, was assumed.

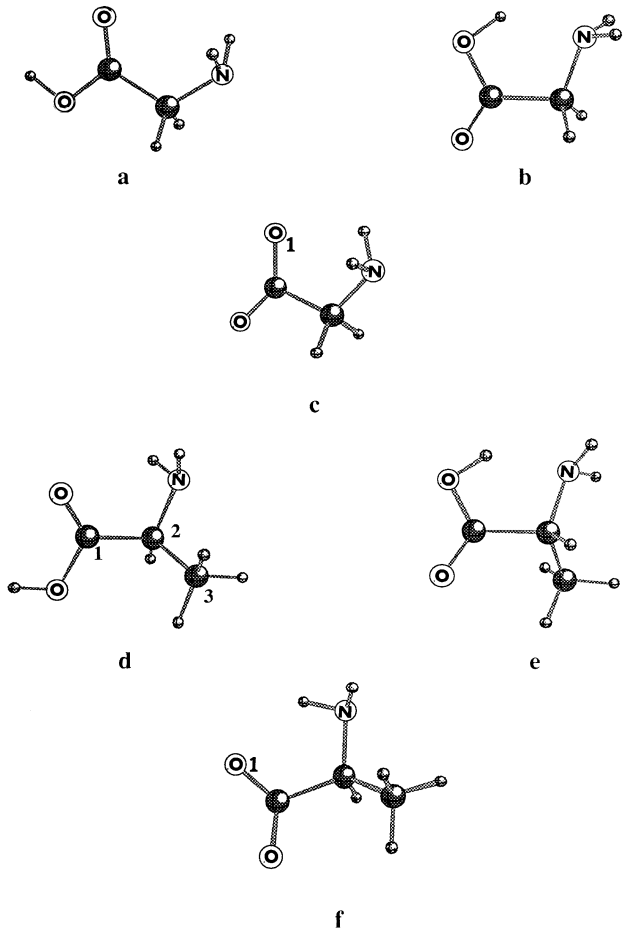


**Figure 1.** Absolute minima for glycine (a) and alanine (d) obtained by both MP2 and B3LYP computations. Absolute minima for glycine (b) and alanine (e) obtained at BP and PWP levels of theory. All computational methods give the same most stable conformation for the anionic form of glycine (c) and alanine (f).

## Results and Discussion

As a first step, we explored the conformations of glycine and alanine, considering the most stable structures resulting from previous studies [25–27]. For both glycine and alanine, MP2 and B3LYP computations gave an absolute minimum with a trans-molecular skeleton with the two amino hydrogens pointing towards the oxygen atom of the C═O group (a and d in Fig. 1). The lowest relative minima of MP2 and B3LYP lie, respectively, at 0.6 and 0.1 kJ/mol for glycine and 3.8 and 2.1 kJ/mol for alanine. A different conformation resulted from the BP and PWP gradient-corrected computations, that is, a *cis* skeleton in which a hydrogen bond between the nitrogen lone pair and the carboxylic hydrogen (b and e in Fig. 1) occurs. In this case a second minimum, with the same conformation as those from MP2 and B3LYP, was found by BP (PWP) computations at 1.0 (4.2) and 3.2 (7.0) kJ/mol for glycine and alanine, respectively. However, no significant influence, deriving from this small energy difference, must be expected for the gas-phase acidity values. The same absolute conformational minimum was found by all the employed methods for both molecules (c and f in Fig. 1).

The optimized geometries, reported in Tables 1 and 2, are in agreement with previous theoretical [25, 27–29] and available experimental data [30, 31]. In particular, the comparison reveals that DF bond lengths and valence angles are always very similar to those obtained at the MP2 level.

The theoretical absolute gas-phase acidities at 298 K ($\Delta G_{acid}$) together with the various contributions [$\Delta E_{el}$, $\Delta$(ZPE), $\Delta H_{acid}$ and $T\Delta$S] are reported in Tables 3 and 4, respectively, for glycine and alanine.

The data in the tables underline the importance of obtaining reliable energy differences ($\Delta E_{el}$) from SCF calculations because, as is evident, the ZPE corrections and the entropic terms ($T\Delta S$) computed explicitly at

**Table 2.** Geometrical parameters of alanine computed at different levels of theory. Distances are in Å and angles in degrees

| Parameter | BP | PWP | B3LYP | MP2 | EXP[a] |
|---|---|---|---|---|---|
| C1–C2 | 1.549 | 1.551 | 1.531 | 1.521 | 1.507 |
| C2–C3 | 1.538 | 1.539 | 1.537 | 1.530 | 1.545 |
| C1═O | 1.220 | 1.219 | 1.205 | 1.211 | 1.192 |
| C1–O | 1.355 | 1.358 | 1.356 | 1.356 | 1.347 |
| C2–N | 1.494 | 1.491 | 1.455 | 1.452 | 1.471 |
| ⟨N–H⟩ | 1.021 | 1.021 | 1.016 | 1.016 | / |
| O–H | 1.004 | 1.007 | 0.969 | 0.968 | / |
| ⟨C3–H⟩ | 1.100 | 1.100 | 1.092 | 1.092 | / |
| C2–H | 1.103 | 1.101 | 1.094 | / | / |
| C1–C2–C3 | 109.1 | 109.0 | 109.2 | 108.3 | 111.6 |
| O–C1–O | 123.5 | 123.5 | 122.6 | 123.1 | 123.8 |
| C2–C1═O | 123.1 | 123.5 | 125.6 | 125.4 | 125.6 |
| C2–C1–O | 113.4 | 113.3 | 111.8 | 111.4 | 110.3 |
| N–C2–C1 | 108.2 | 108.3 | 113.6 | 113.7 | 110.1 |
| ⟨H–C3–C2⟩ | 110.6 | 110.6 | 110.0 | / | / |
| ⟨–N–C2⟩ | 111.8 | 111.9 | 110.2 | 109.2 | / |
| C1–O–H | 103.5 | 103.4 | 107.5 | 106.2 | / |

[a]From [30].

**Table 3.** Absolute gas phase acidity of glycine calculated at different levels of theory. Experimental values are taken from [3]. $\Delta(\Delta H_{acid})=\Delta H_{acid\ calc}-\Delta H_{acid\ exp}$ and $\Delta(\Delta G_{acid})=\Delta G_{acid\ calc}-\Delta G_{acid\ exp}$. All values are in kJ/mol.

| Method | $\Delta E_{el}$ | Δ(ZPE) | $\Delta H_{acid}$ | $\Delta(\Delta H_{acid})$ | $T\Delta S$ | $\Delta G_{acid}$ | $\Delta(\Delta G_{acid})$ |
|---|---|---|---|---|---|---|---|
| HF/6-31G(*d*)-opt | 1514.9 | 33.7 | 1487.1 | 56.1 | 33.0 | 1454.1 | 52.0 |
| MP2/6-31G(*d*)-opt | 1492.0 | 33.7 | 1464.5 | 33.5 | 33.0 | 1431.5 | 29.5 |
| MP2/6-311+G(3*df*,2*p*) | 1449.4 | 33.7 | 1421.9 | −9.1 | 33.0 | 1388.9 | −13.1 |
| QCISD(*T*)/6-311G(*d*,*p*) | 1519.0 | 33.7 | 1491.5 | 60.5 | 33.0 | 1458.5 | 56.5 |
| MP4/6-311G(*d*,*p*) | 1515.2 | 33.7 | 1487.7 | 56.7 | 33.0 | 1454.7 | 52.7 |
| MP4/6-311+G(*d*,*p*) | 1466.2 | 33.7 | 1438.7 | 7.7 | 33.0 | 1405.7 | 3.7 |
| MP4/6-311G(2*df*,*p*) | 1496.3 | 33.7 | 1468.8 | 37.8 | 33.0 | 1435.8 | 33.8 |
| G2 | 1457.4 | 33.7 | 1430.0 | −1.0 | 33.0 | 1397.0 | −5.0 |
| B3LYP/6-311+G(*d*,*p*)-opt | 1453.5 | 35.3 | 1424.4 | −6.6 | 34.6 | 1389.8 | −12.2 |
| PWP-TZ+−opt | 1448.0 | 33.6 | 1420.8 | −10.2 | 32.9 | 1387.9 | −14.1 |
| BP-TZ+−opt | 1470.7 | 33.6 | 1443.5 | 12.5 | 32.9 | 1410.6 | 8.6 |
| EXP | / | / | 1431.0 | / | 29.0 | 1402.0 | / |

HF, B3LYP, PWP, and BP levels differ at most by 2.1 kJ/mol.

Ab initio $\Delta E_{el}$ values depend on the correlation contributions, but more importantly, on the choice of the basis set. The former effect is revealed by the difference between HF/6-31G(*d*) and MP2/6-31G(*d*) $\Delta E_{el}$ values (1514.9 versus 1492.0 kJ/mol for glycine and 1512.3 versus 1488.0 kJ/mol for alanine). To confirm the stronger effect of the basis set, we note the MP4 results. For both molecules, the addition of *f* functions reduces by about 17–21 kJ/mol the $\Delta E_{el}$, whereas the presence of a diffuse function is sufficient to lower the energy differences by 46–50 kJ/mol.

The influence of the addition of both *f* and diffusion functions emerges clearly in the comparison between MP2/6-311+G(3*df*,2*p*) and MP2/6-31G(*d*) results (see Tables 3 and 4). On the basis of this evidence, gradient-corrected calculations were performed by using only a triple zeta basis set with diffuse functions. The values for $\Delta H_{acid}$ and $\Delta G_{acid}$ from higher level theoretical data are closer to the experimental ones.

Taking as reference the $\Delta H_{acid}$ and $\Delta G_{acid}$ measured values [3] of 1431.0 and 1402.0 kJ/mol for glycine and 1427.5 and 1398.5 kJ/mol for alanine, we discuss separately our best results. The G2 procedure gives a difference of −1.0 and −5.1 kJ/mol between the experimental and theoretcal values for $\Delta H_{acid}$ and $\Delta G_{acid}$ in the case of glycine and 0.2 and −3.6 kJ/mol for alanine.

At the MP2/6-311+G(3*df*,2*p*) level, we obtained $\Delta H_{acid}$ values that are different from the experimental ones by −9.1 and −8.1 kJ/mol and $\Delta G_{acid}$ deviations of −13.1 and −11.8 kJ/mol for glycine and alanine, respectively.

The deviations resulting from B3LYP hybrid functional use are −6.6 ($\Delta H_{acid}$) and −12.2 kJ/mol ($\Delta G_{acid}$) for glycine and −5.0 ($\Delta H_{acid}$) and −10.3 kJ/mol ($\Delta G_{acid}$) for alanine.

The gradient-corrected PWP functional gives differences of −10.2 ($\Delta H_{acid}$) and −14.1 kJ/mol ($\Delta G_{acid}$) for glycine and −10.1 ($\Delta H_{acid}$) and −13.7 kJ/mol ($\Delta G_{acid}$) for alanine. Finally, the BP $\Delta H_{acid}$ and $\Delta G_{acid}$ values deviate from the experimental ones by 12.5 and 8.6 kcal/mol for glycine and 3.7 and 0.1 kJ/mol for alanine.

The different small errors that occur in the $\Delta H_{acid}$ and $\Delta G_{acid}$ estimations are connected with the level of accuracy, given for each method, in the reproduction of vibrational and entropic contributions. Furthermore, slight differences in the evaluation of Δ(ZPE) and $T\Delta S$ occur for the various methods. It is worth noting that the experimental $\Delta G_{acid}$ was obtained by assuming a fixed $T\Delta S$ (29.0 kJ/mol) that is lower than all other calculated values for both molecules.

**Table 4.** Absolute gas phase acidity of alanine calculated at different levels of theory. Experimental values are taken from [3]. $\Delta(\Delta H_{acid})=\Delta H_{acid\ calc}-\Delta H_{acid\ exp}$ and $\Delta(\Delta G_{acid})=\Delta G_{acid\ calc}-\Delta G_{acid\ exp}$. All values are in kJ/mol.

| Method | $\Delta E_{el}$ | Δ(ZPE) | $\Delta H_{acid}$ | $\Delta(\Delta H_{acid})$ | $T\Delta S$ | $\Delta G_{acid}$ | $\Delta(\Delta G_{acid})$ |
|---|---|---|---|---|---|---|---|
| HF/6-31G(*d*)-opt | 1512.3 | 33.9 | 1484.6 | 57.1 | 33.9 | 1451.8 | 51.2 |
| MP2/6-31G(*d*)-opt | 1488.0 | 33.9 | 1460.3 | 32.8 | 33.9 | 1427.6 | 29.1 |
| MP2/6-311+G(3*df*,2*p*) | 1447.1 | 33.9 | 1419.4 | −8.1 | 33.9 | 1386.7 | −11.8 |
| QCISD(*T*)/6-311G(*d*,*p*) | 1512.9 | 33.9 | 1485.2 | 57.7 | 33.9 | 1452.5 | 54.0 |
| MP4/6-311G(*d*,*p*) | 1508.9 | 33.9 | 1481.2 | 53.7 | 33.9 | 1448.4 | 49.9 |
| MP4/6-311+G(*d*,*p*) | 1464.1 | 33.9 | 1436.5 | 9.0 | 33.9 | 1403.7 | 5.2 |
| MP4/6-311G(2*df*,*p*) | 1490.5 | 33.9 | 1462.8 | 35.3 | 33.9 | 1430.0 | 31.5 |
| G2 | 1455.4 | 33.9 | 1427.7 | 0.2 | 33.9 | 1394.9 | −3.6 |
| B3LYP/6-311+G(*d*,*p*)-opt | 1452.4 | 36.1 | 1422.5 | −5.0 | 34.3 | 1388.2 | −10.3 |
| PWP-TZ+−opt | 1446.0 | 35.1 | 1417.4 | −10.1 | 32.6 | 1384.8 | −13.7 |
| BP-TZ+−opt | 1459.8 | 35.1 | 1431.2 | 3.7 | 32.6 | 1398.6 | 0.1 |
| EXP | / | / | 1427.5 | / | 29.0 | 1398.5 | / |

To build a relative scale of acidities ($\Delta G_{acid}$) of $\alpha$-amino acids, it is of interest to examine how the acidity gap between glycine and alanine was reproduced. In this case, the various methods give accurate differences. The best results are obtained at MP2 (2.2 kJ/mol), MP4 (2.0 kJ/mol), G2 (2.0 kJ/mol), and PWP (3.1 kJ/mol) levels. BP seems to overestimate this quantity (12.0 kJ/mol). The experimental difference is 3.5 kJ/mol.

The decision for the best theoretical result is not simple to take because the experimental data have some uncertainty (they are subjected to an error of approximately 15%) [3]. Thus, we can only suggest there is good agreement between the results of high level calculations and measured values. Nevertheless, some aspects must be emphasized. Because G2, MP2, B3LYP, PWP, and BP gas-phase acidities are all characterized by an accuracy within 17 kJ/mol, we can address which method allows the better compromise between reliability and computational demands. There is no doubt that density functional methods represent the best tools for obtaining gas-phase acidity for medium–large sized molecular systems.

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