

# Predicting Deprotonation Sites Using Alchemical Derivatives


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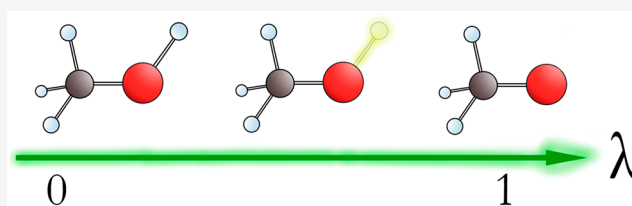
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**ABSTRACT:** An alchemical transformation is any process, physical or fictitious, that connects two points in the chemical space. A particularly important transformation is the vanishing of a proton, whose energy can be linked to the proton dissociation enthalpy of acids. In this work we assess the reliability of alchemical derivatives in predicting the proton dissociation enthalpy of a diverse series of mono- and polyprotic molecules. Alchemical derivatives perform remarkably well in ranking the proton affinity of all molecules. Additionally, alchemical derivatives could be used also as a predictive tool because their predictions correlate quite well with calculations based on energy differences and experimental values. Although second-order alchemical derivatives underestimate the dissociation enthalpy, the deviation seems to be almost constant. This makes alchemical derivatives extremely accurate to evaluate the difference in proton affinity between two acid sites of a polyprotic molecule. Finally, we show that the reason for the underestimation of the dissociation enthalpy is most likely the contribution of higher-order derivatives.



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## INTRODUCTION

Methods in quantum chemistry have achieved a remarkable accuracy in calculating energy differences and linear response properties for molecules of tens of atoms. However, the in silico design of a new molecule with special characteristics is a very complex computational task. The main reason for this lies in the immensity of the chemical space; the chemical space encompasses the set of all possible molecules given the number of atoms and their nuclear charges.<sup>1–5</sup> The number of possible molecules is giant. The number of molecules that can be formed with up to 20 atoms and nuclear charges corresponding to typical organic molecules is about  $10^{60}$ .<sup>6,7</sup>

Of course, the number of stable molecules is much smaller but still out of the range of applications of electronic structure methods. Therefore, it is impossible to think of scanning the whole space in the search for a specific molecule. However, a perturbative method known as alchemical transformations<sup>8–13</sup> significantly reduces the exploration of sectors of the chemical space. Briefly, an alchemical transformation is any transformation that connects any two points in the chemical space.<sup>3,10,13–15</sup> Alchemical transformations do not necessarily correspond to physical processes, although some of them do, which is the case of the deprotonation of a molecule. The energy change that comes with an alchemical transformation can be estimated with perturbation theory. From density functional theory one knows that the energy of an electronic system is a function of the number of electrons,  $N$ , and a functional of the external potential,  $\delta v(r)$ .<sup>16</sup> Hence, the energy change of an alchemical transformation matches the energy variation under appropriated variations of the number of

electrons and/or the external potential.<sup>17</sup> As an example, a variation in the number of electrons could be the estimation of the ionization energy, and a variation of the atomic number of a hydrogen nucleus could be the estimation of the deprotonation energy.<sup>18</sup> It is also possible, and more usual, to have both perturbations at the same time.<sup>19</sup> Despite the complexity of exploring the chemical space, striking achievements have been accomplished within the scheme of alchemical transformations/derivatives. For instance, Paul Geerlings and his collaborators have shown the usefulness of alchemical derivatives to explore the energy landscape of transformations of increasing difficulty such as deprotonation and substitution of isoelectronic C–C and C–H units in organic molecules<sup>20</sup> and the extremely complex problem of computing all possible B–N substitutions on a C<sub>60</sub> fullerene.<sup>21</sup> Nowadays, it is possible to evaluate alchemical derivatives of all atoms<sup>22</sup> and alchemical transmutations along the periodic table.<sup>23</sup>

In this work we will use alchemical transformations and perturbation theory to predict the deprotonation site of monoprotic organic molecules, ammoniums, carboxylic acids, and aromatic molecules. We will also work on polyprotic molecules, pyrimidines, and purines.

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## ■ THEORETICAL BACKGROUND AND COMPUTATIONAL DETAILS

An alchemical transformation that changes the composition of a parent system, through mutation of atoms, will result in a change in the external potential, and the number of electrons, in the Hamiltonian. Therefore, the energy change, including nuclear repulsion, for a nondegenerate ground state,<sup>24–26</sup> can be expressed as a Taylor series, which at second-order reads

$$\begin{aligned} \Delta W[N, v(\mathbf{r})] &= \left(\frac{\partial W}{\partial N}\right)_v \Delta N + \int d\mathbf{r} \left(\frac{\delta W}{\delta v(\mathbf{r})}\right)_N \delta v(\mathbf{r}) \\ &+ \int d\mathbf{r} \frac{\delta^2 W}{\partial N \delta v(\mathbf{r})} \delta v(\mathbf{r}) \Delta N + \frac{1}{2} \left(\frac{\partial^2 W}{\partial N^2}\right)_v \\ &(\Delta N)^2 + \frac{1}{2} \int d\mathbf{r} d\mathbf{r}' \left(\frac{\delta^2 W}{\delta v(\mathbf{r}) \delta v(\mathbf{r}')}\right)_N \delta \\ &v(\mathbf{r}) \delta v(\mathbf{r}') + \sum_{l+n=3} O((\Delta N)^l (\delta v)^n) \end{aligned} \quad (1)$$

In an alchemical transformation the variation of the external potential consists only in a change of the atomic number of the transmuted atoms. Therefore, eq 1 can be written in terms of alchemical derivatives, that is to say the derivative of the energy with respect to the atomic numbers,  $Z_\beta$ ,

$$\begin{aligned} \Delta W[N, v(\mathbf{r})] &= \left(\frac{\partial W}{\partial N}\right)_v \Delta N + \sum_\beta \left(\frac{\partial W}{\partial Z_\beta}\right)_N \Delta Z_\beta \\ &+ \sum_\beta \left(\frac{\partial^2 W}{\partial Z_\beta \partial N}\right)_N \Delta Z_\beta \Delta N + \frac{1}{2} \left(\frac{\partial^2 W}{\partial N^2}\right)_v \\ &(\Delta N)^2 + \frac{1}{2} \sum_{\beta, \alpha} \left(\frac{\partial^2 W}{\partial Z_\beta \partial Z_\alpha}\right)_N \Delta Z_\beta \Delta Z_\alpha \\ &+ \sum_{l+n=3} O((\Delta N)^l (\Delta Z)^n) \end{aligned} \quad (2)$$

In the jargon of conceptual density functional theory,<sup>27–32</sup> eq 2 can be written, after splitting the total energy in electronic and nuclear repulsion, as

$$\begin{aligned} \Delta W[N, v(\mathbf{r})] &= \mu \Delta N + \int d\mathbf{r} \rho(\mathbf{r}) \delta v(\mathbf{r}) \\ &+ \int d\mathbf{r} f(\mathbf{r}) \delta v(\mathbf{r}) \Delta N + \frac{1}{2} \eta (\Delta N)^2 \\ &+ \frac{1}{2} \int d\mathbf{r} d\mathbf{r}' \chi(\mathbf{r}, \mathbf{r}') \delta v(\mathbf{r}) \delta v(\mathbf{r}') + \Delta V_{NN} \\ &+ \sum_{l+n=3} O((\Delta N)^l (\delta v)^n) \end{aligned} \quad (3)$$

where the parameters of the Taylor series expansion have been identified as the electronic chemical potential  $\mu$ ,<sup>33</sup> the electron density  $\rho(r)$ , the Fukui function  $f(r)$ ,<sup>34–36</sup> the electronic hardness  $\eta$ ,<sup>37–39</sup> and the linear response function  $\chi(r, r')$ .<sup>40,41</sup> The last term  $\Delta V_{NN}$  corresponds to the variation of the nuclear repulsion, which in the Born–Oppenheimer approximation is just a parameter.

It is important to note that all the derivatives of the series are properties of the unperturbed system. Hence, the energy change in an alchemical transformation could be in principle predicted with just a single point calculation once the

perturbation has been identified. The convergence of the series has been studied by Ayers et al.<sup>17</sup> They found that the series converge until the perturbation changes the ground state of the unperturbed system. Numerical results show that the evaluation of the series to second-order of perturbation, eq 2, is enough for most chemical applications.<sup>42,43</sup> A deeper analysis of the series and the details of the calculations of each term can be found in our previous work.<sup>19</sup> The proton dissociation enthalpy has been calculated as

$$PA = \Delta W + \Delta E_{\text{vib}} + \frac{5}{2} RT \quad (4)$$

where the first term represents the electronic and nuclear repulsion energy changes calculated through two methods, the alchemical derivatives<sup>19</sup>

$$\begin{aligned} \Delta W_{\text{elec+nn}}^{\text{alchem}} &= \left(\frac{\partial W}{\partial Z_H}\right)_N \Delta Z_H + \frac{1}{2} \left(\frac{\partial^2 W}{\partial Z_H^2}\right)_N \Delta Z_H^2; \Delta Z_H \\ &= -1 \end{aligned} \quad (5)$$

and with the energy difference between the protonated and deprotonated molecule. The second term in eq 4 corresponds to the zero point vibration energy, and the last one is the translational energy plus the  $RT$  term presented in enthalpy of an ideal gas. Since the last term is much smaller than others the ideal gas approximation is sufficient. Changes in rotational energy are neglected because rotational energy is much smaller than thermal energy ( $k_B T$ ) at room temperature. Note that the proton affinity is the negative of the enthalpy change in the gas phase reaction between a proton and the chemical species concerned, to give the conjugate acid of that species. Here we model the reverse process, the removal of a proton from the conjugate acid.

The energy, the optimization of the geometries, and the vibrational frequencies have been calculated using two different exchange correlation functionals, the hybrid functional B3LYP and the long-range corrected  $\omega$ -B97XD functional. The employed bases set were the def2-TZVPPD and the cc-pVTZ. The differences in results among them are small, therefore, we will show only the results obtained with B3LYP/def2-TZVPPD. All calculations were done with the Gaussian09 program.<sup>44</sup> Alchemical derivatives were computed using finite differences (see the Supporting Information) in a recent implementation of ChemTools<sup>35</sup> module of HORTON,<sup>46</sup> which is dedicated to computing chemical response functions.

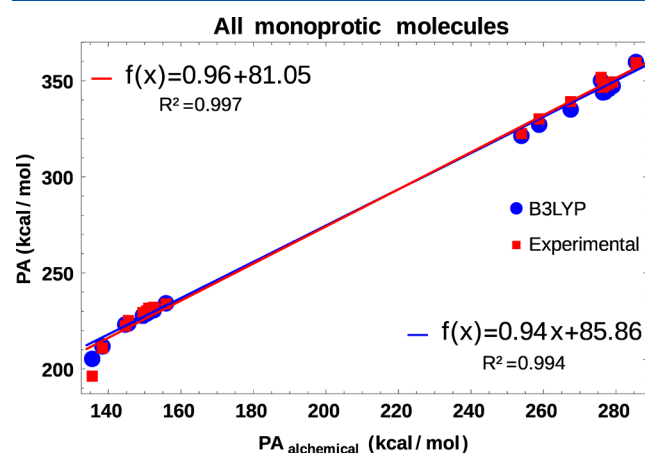
## ■ RESULTS AND DISCUSSION

In Table 1 some results are presented. Namely, the proton dissociation enthalpy calculated using the alchemical derivatives, the B3LYP calculation using the energy difference between the protonated and deprotonated molecule, and the experimental proton affinity, which is numerically equal to the proton dissociation enthalpy. First, notice that the B3LYP calculations are in excellent agreement with experimental results. Therefore, the employed methodology is suitable. Looking at the calculations using the alchemical derivatives, one can observe a systematic difference (which will be discussed later) with the B3LYP calculations of around 70–80 kcal/mol. In favor of the presented alchemical results one can see that the ranking of the molecules according to their proton dissociation enthalpy is the correct one for the three families of molecules, which are quite diverse in terms of

**Table 1. Proton Dissociation Enthalpy (kcal/mol) Obtained by Alchemical Derivatives, Energy Differences with B3LYP/def2-TZVPPD, and Experimental Values<sup>47–49</sup>**

Proton Dissociation Enthalpy			
	alchemical	B3LYP	experimental
Ammoniums			
<i>N</i> -methyletanammonium	145.6	224.9	225.2
<i>N,N</i> -dimethyletanammonium	149.6	228.9	229.4
<i>N,N</i> -dimethylpropanammonium	150.6	230.0	230.1
<i>N,N</i> -dimethylbutanammonium	151.2	230.7	231.6
<i>N</i> -ethyl- <i>N</i> -methylpropanammonium	152.6	231.8	232.1
Aromatic			
benzoic acid	135.6	206.5	196.2
anilinium	138.5	213.0	210.9
pyridinium	144.7	224.3	222.3
indolinium	275.9	351.3	351.8
phenol	279.2	348.5	349.4
pyrrolidinium	285.6	361.0	359.5
Carboxylic Acids			
trifluoroacetic acid	254.0	322.6	322.6
difluoroacetic acid	258.9	328.4	330.2
fluoroacetic acid	267.6	336.3	339.2
butanoic acid	276.5	345.2	346.6
propanoic acid	277.0	345.4	347.5
ethanoic acid	278.1	345.2	346.6

proton transfer affinities. Amines acting as a Brønsted–Lowry bases accepting a proton, carboxylic acids losing a proton, and aromatic molecules acting as bases or acids. The correlation between the alchemical results and the energy differences (B3LYP) and experimental ones for all the studied molecules is good, as it can be seen from Figure 1. The regression of



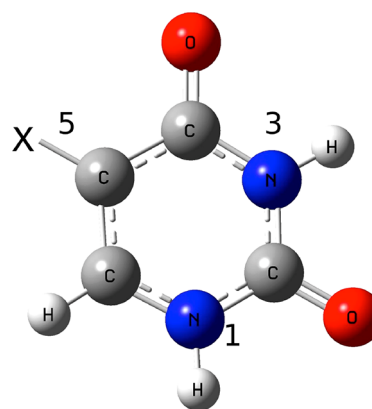
**Figure 1.** Regression of proton dissociation enthalpy of molecules in Table 1 against values predicted with alchemical derivatives. Two sets of data are plotted: values computed as energy differences with B3LYP and experimental values.

experimental and alchemical values is remarkable:  $PA_{\text{exp}} = 0.94PA_{\text{alchem}} + 85.86$ , with correlation coefficient  $R^2 = 0.994$ , indicating the notable performance of the alchemical derivatives in ranking the molecules according to their proton dissociation enthalpy despite the wide range of values in the set of molecules (196–359 kcal/mol). If regressions are done for each family separately, the fitting does not worsen:  $PA_{\text{exp}} = 0.85PA_{\text{alchem}} + 102.02$ ;  $R^2 = 0.952$  for ammoniums,  $PA_{\text{exp}} =$

$1.03PA_{\text{alchem}} + 63.39$ ;  $R^2 = 0.991$  for carboxylic acids, and  $PA_{\text{exp}} = 1.02PA_{\text{alchem}} + 66.61$ ;  $R^2 = 0.952$  for aromatic compounds.

Now, we will show the results for the most challenging case of some representative polyprotic molecules. Those are molecules able to donate more than one proton from different sites. An important group of polyprotic molecules are the pyrimidines and the purines. Uracils are pyrimidine derivatives with two nitrogen atoms as it is shown in the Scheme 1, where

**Scheme 1.** Uracils with Two Deprotonation Sites  $N_1$  and  $N_3$ <sup>a</sup>

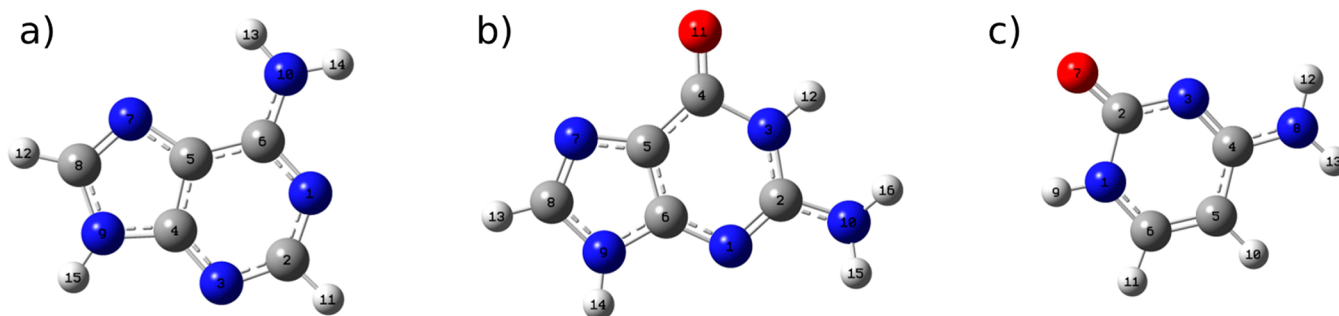


<sup>a</sup>Substituents in position 5 are X = CH<sub>3</sub>, H, F, CHO, and NO<sub>2</sub>.

the nitrogen atoms are labeled as  $N_1$  and  $N_3$  for the next discussion. Substituents in position 5 are X = CH<sub>3</sub>, H, F, CHO, and NO<sub>2</sub>. The purines are molecules formed by a six atoms ring and a five atoms ring with four nitrogen atoms and three or more deprotonation sites. The most important of them are the ones presented in the DNA. Here, we will study, in particular, the adenine, the guanine and the cytosine, shown in Scheme 2.

Table 2 lists the proton dissociation enthalpy calculated with the alchemical derivatives and the B3LYP values together with the experimental ones. Again one can observe the perfect agreement of the B3LYP values with the experimental ones. The values using the alchemical derivatives differ by approximately 70 kcal/mol with respect to the B3LYP and experimental values. Hence, the correlation between them is very good ( $PA_{\text{B3LYP}} = 1.03PA_{\text{alchem}} + 66.27$ ) with a correlation coefficient  $R^2 = 0.994$ . But more important than the absolute value it is the prediction of the site of deprotonation. One can see that the relative order in each of the studied molecules is the same for the alchemical calculations and the B3LYP ones. Note that the predicted differences are on the order of a couple of kcal/mol. This implies a very high accuracy in the use of the alchemical derivatives. The main consequence of this is not to expect from the alchemical derivatives a perfect match with the experimental or calculated proton affinities but a very high predictive character of the sites and energy ranking of the deprotonation. The computational time can be drastically reduced when analytical derivatives are used as in ref 43. For a molecule with  $n$  protonation sites, the number of electronic structure calculations needed to compute the  $PA$  would be  $2n + 2$ , against only one calculation using the alchemical derivatives. Despite that, it is interesting to analyze the reason of the almost constant deviation of around 70 kcal/mol in the absolute values.

Scheme 2. Polyprotic Molecules with Three or More Deprotonation Sites: (a) Adenine, (b) Guanine, and (c) Cytosine

Table 2. Proton Dissociation Enthalpy (kcal/mol) of Polyprotic Molecules Obtained by the Alchemical Derivatives, Energy Differences with B3LYP/def2-TZVPPD, and Experimental Values<sup>50</sup>

molecule	Proton Dissociation Enthalpy			
	site	alchemical	B3LYP	experimental
thymine	N <sub>1</sub> -H	263.1	336.2	333(2)
	N <sub>3</sub> -H	270.4	347.5	347(4)
uracil	N <sub>1</sub> -H	261.7	334.6	333(2)
	N <sub>3</sub> -H	273.7	347.0	347(2)
5-fluorouracil	N <sub>1</sub> -H	256.8	329.5	329(3)
	N <sub>3</sub> -H	267.1	340.4	
<i>trans</i> -5-formyluracil	N <sub>1</sub> -H	247.3	320.9	
	N <sub>3</sub> -H	262.5	335.3	
<i>cis</i> -5-formyluracil	N <sub>1</sub> -H	246.6	319.9	
	N <sub>3</sub> -H	264.1	336.8	
5-nitouracil	N <sub>1</sub> -H	240.2	314.2	
	N <sub>3</sub> -H	257.4	329.9	
adenine	N <sub>9</sub> -H	264.5	339.7	333(1)
	NH-H	288.2	357.3	352(2)
	NH-H	287.9	357.6	352(2)
	C <sub>2</sub> -H	329.1	402.3	
guanine	N <sub>9</sub> -H	300.1	376.4	
	NH-H	264.7	338.5	331(4)
	NH-H	278.3	344.4	336(4)
	NH-H	272.2	339.7	337(4)
cytosine	N <sub>3</sub> -H	267.4	340.5	334(4)
	C <sub>8</sub> -H	304.8	380.2	
	N <sub>1</sub> -H	274.3	348.9	340(2)
	NH-H	286.4	355.6	346(4)
	NH-H	282.6	350.6	346(4)
	C <sub>5</sub> -H	304.2	379.6	
	C <sub>6</sub> -H	295.7	372.1	

Figure 2 shows the alchemical transformation of the methanol to the methoxyl anion. The path of the transformation is an especial one. Without change the geometry of the methanol the charge of the hydrogen bonded to the oxygen atom has been varied from one to zero. In this way, the only perturbation is in the nuclear charge that goes from one to zero with steps of 0.1. The energy of these states is represented by the blue points, and the zero of energy has been taken as the methanol's energy. The calculated proton affinity along this adiabatic path is 380 kcal/mol. The energy difference with the optimized geometry for the methoxyl anion is only 4 kcal/mol. Hence, the relaxation energy cannot explain the discussed deviation of around 70 kcal/mol. Then the curve has been fitted with third-order polynomials in  $Z_H$ . The blue curve corresponds to the energy path predicted by eq 5. That is,

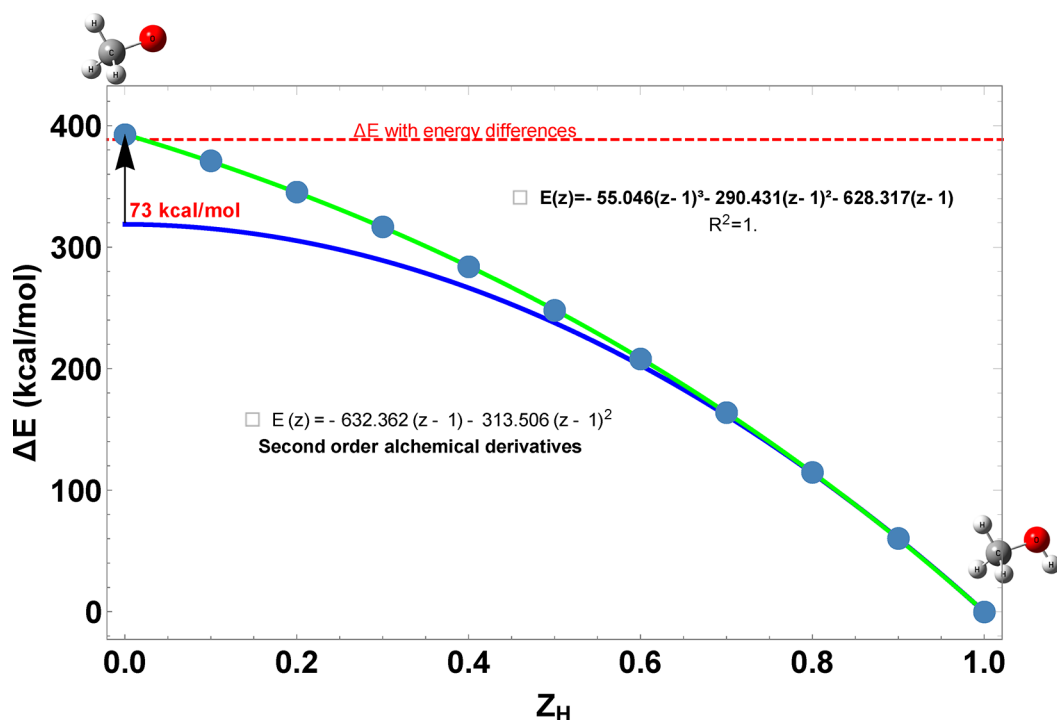
including alchemical derivatives up to second-order. Note that the linear and quadratic coefficients of the cubic interpolation are in good agreement with first- and second-order alchemical derivatives (coefficients of the blue curve). The cubic term in the third order polynomial alone is responsible for 55 kcal/mol of the deviation. This could be a signature of the importance of the third order derivatives in the expansion.<sup>51</sup> Indeed, as we used backward finite differences with third-order accuracy in the step ( $O(\Delta Z^3)$ ), the same data can be used to estimate the third-order alchemical derivative with ( $O(\Delta Z^2)$ ) accuracy. The estimated proton dissociation energies of all monoprotic and polyprotic molecules are reported in Tables S1 and S2 in the Supporting Information, respectively. The main result can be summarized as an improvement in the quality of the regression between experimental proton affinities and their alchemical estimation:  $PA_{\text{exp}} = 0.995PA_{\text{alchem}} - 23.34$  ( $R^2 = 0.993$ ) for monoprotic molecules and  $PA_{\text{exp}} = 0.842PA_{\text{alchem}} + 36.93$  ( $R^2 = 0.821$ ) for polyprotic ones. Inclusion of third-order derivatives results in an overestimation of the experimental dissociation energy of ca. 25 and 28 kcal/mol for mono- and polyprotic molecules, respectively. This overestimation is to be compared with the subestimation of ca. 86 and 70 kcal/mol for both sets of molecules when derivatives up to second-order are used.

The discrepancy between alchemical predictions and experiments can be partially attributed to the sum of (i) basis set superposition error, (ii) Pulay's error because the optimal exponents of the Gaussian basis must depend on the atomic charge, and (iii) the slow convergence of the Taylor series expansion in the case of hydrogen.<sup>36</sup> All these effects were deeply discussed by Balawender et al.<sup>20</sup>

## CONCLUSIONS

The chemical space holds all possible compounds that can be imagined. Its colossal size rules out the possibility of computing the properties of its elements with ab initio calculations. But, only a small fraction of these compounds have practical interest. Besides, only few paths in the chemical space correspond to actual chemical process. One of those paths is the adiabatic elimination of an acid proton. The change of energy along that path is related to the proton dissociation enthalpy (eq 4). Alchemical derivatives allow predicting the electronic contribution to it. Here we use alchemical derivatives, including derivatives up to second order (eq 5) to assess how reliable alchemical derivatives are in predicting the proton dissociation enthalpy of a diverse series of mono- and polyprotic molecules. Alchemical derivatives perform remarkably well in ranking the proton affinity of all molecules. Additionally, alchemical derivatives could be used also as a predictive tool because their predictions correlate





**Figure 2.** Adiabatic path of the alchemical transformation of methanol into methoxyl anion. Blue points correspond to actual B3LYP/def2-TZVPPD calculation with fractional charge of the acid proton of methanol. The green curve is a third-order polynomial fit. The blue curve is the path predicted with alchemical derivatives up to second-order (eq 5). The dashed red line is the difference in energy between methanol and methoxyl computed with energy differences. The zero of the energy is set in the methanol energy.

quite well with calculations based on energy differences ( $R^2 = 0.997$ ) and experimental values ( $R^2 = 0.994$ ). Although second-order alchemical paths underestimate the proton dissociation enthalpy, the deviation seems to be always in the same order (70 kcal/mol). This makes alchemical derivative extremely accurate to evaluate the difference in proton affinity between two acid sites of the same molecule (error is less than 3 kcal/mol in average). Finally, the adiabatic transmutation of methanol into methoxyl allows understanding that the largest part of the underestimation comes from neglecting higher orders of the alchemical derivatives.

## ■ ASSOCIATED CONTENT

### SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.jpca.9b09472>.

Description of the method used to compute alchemical derivatives, comparison of the proton dissociation enthalpy of mono- and polyprotic molecules obtained with alchemical derivatives of up to second and third orders (PDF)

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## Notes

The authors declare no competing financial interest.

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