

# Comment on “On the Accuracy of the Direct Method to Calculate $pK_a$ from Electronic Structure Calculations”

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In a recent publication on the quantum chemistry prediction of  $pK_a$  values for acids,<sup>1</sup> a “direct” method was presented that employed derived values for  $G_{aq}(H^+)$ , and a comparison was made of these derived  $G_{aq}(H^+)$  values to literature ones. We would like to make three corrections to their  $G_{aq}(H^+)$  value comparison and then comment on their method.

First, ref 1 appears to have erred in comparing their Table 5  $G_{aq}(H^+)$  values, the Gibbs energy of the solvated proton, to target literature values for  $\Delta_s G(H^+)$ , the Gibbs energy of solvation (“solvation energy”) of the proton. The relation between the two is  $G_{aq}(H^+) = G_{gas}(H^+) + \Delta_s G(H^+)$ , where  $G_{gas}(H^+) = \frac{5}{2}RT - TS_{Sackur-Tetrode} = -6.3 \text{ kcal mol}^{-1}$  at 298 K temperature and 1 atm pressure.<sup>2</sup>

Second, we are concerned about the authors’ stated belief that the true value of  $\Delta_s G(H^+)$  (and thus of  $G_{aq}(H^+)$ ) is not known to any better than a 19 kcal mol<sup>-1</sup> range of -252.6 to -271.7 kcal mol<sup>-1</sup>. They quoted a 2005 Tanako and Houk paper<sup>3</sup> for this statement and/or range, but we find no such comment there. This claim of large uncertainty fails to recognize the major advance in narrowing the accuracy on  $\Delta_s G(H^+)$ , and thus  $G_{aq}(H^+)$ , made by Coe and co-workers in analyzing gas-phase clustering data. After Coe’s initial narrowing of the  $\Delta_s H(H^+)$  uncertainty in 1994,<sup>4</sup> his Tissandier et al. collaboration<sup>5</sup> produced in 1998 a value of  $\Delta_s G^\circ(H^+) = -264.0 \text{ kcal mol}^{-1}$  (1 atm gas  $\rightarrow$  1 M aqueous convention), which has been fully supported by altered or improved determinations ever since (for instance -263.7,<sup>6</sup> -263.8,<sup>7</sup> -264.2,<sup>8</sup> -263.4<sup>9</sup> kcal mol<sup>-1</sup>). We support the 2005 recommendation of Camaioni and Schwerdtfeger<sup>10</sup> that the 1998 Tissandier et al. value of  $\Delta_s G^\circ(H^+)$  be accepted as the anchoring value for ion solvation energies, with the understanding that this value has uncertainty that is likely greater than 1 kcal mol<sup>-1</sup>,<sup>9</sup> but quite unlikely to be as large as implied by ref 1. Extending to 1 M gas conventions and full  $G_{aq}$  values, the set of Gibbs energies for aqueous  $H^+$  appears in Table 1.

Table 1. Gibbs Energy Values for  $H^+$  (kcal mol<sup>-1</sup>), 1998 Anchoring<sup>5</sup>

concn convention	$G_{gas}$	$\Delta_s G$	$G_{aq(1M)}$
<sup>o</sup> (1 atm gas, 1 M aq)	$G_{gas}^\circ = -6.3$	$\Delta_s G^\circ = -264.0$	$G_{aq} = -270.3$
<sup>*</sup> (1 M gas, 1 M aq)	$G_{gas}^* = -4.4$	$\Delta_s G^* = -265.9$	$G_{aq} = -270.3$

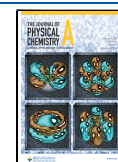
Third, using Table 1, one can reinterpret the derived  $G_{aq}(H^+)$  results of Table 5 of ref 1 and see that the better  $G_{aq}(H^+)$  predictions come from LSDA/SMD, not G4CEP/SMD. The half-reaction  $\Delta_h G_{aq}$  errors made by the SMD continuum model are apparently partially canceled by the electronic errors made by the poor LSDA model, vis-a-vis the presumably more accurate G4CEP electronic model.

As for what to do about the remaining errors from a quantum chemistry model like either LSDA/SMD or G4CEP/SMD, we next offer comments on the direct-method approach of ref 1. By “direct method” they mean the use of a consistent value for  $G_{aq}(H^+)$  and quantum-chemistry-with-continuum-solvation computation of the relevant conjugate acid/base half-reaction,  $\Delta_h G_{aq}(HA \rightarrow A^-) = G_{aq}(A^-) - G_{aq}(HA)$  or  $\Delta_h G_{aq}(HB^+ \rightarrow B) = G_{aq}(B) - G_{aq}(HB^+)$ . The previous literature cases they cited,<sup>2,11,12</sup> as well as our own SHE procedure,<sup>13</sup> employed estimates of the true experimental  $H^+$  values, which exposes the computational error made on the half-reaction. In our case these were errors of roughly 0.7 and 1.7  $pK_a$  units (1.0 and 2.3 kcal mol<sup>-1</sup>) for acyclic and cyclic amines, respectively, which then became empirical external corrections in future predictions (the SHE method).

However, the direct-method approach employed in ref 1 instead uses empirical *internal* correction, placing the correction inside the value used for  $G_{aq}(H^+)$ . Our first point is that this idea is not new; we had tried it in 2008–2009,<sup>14</sup> following the lead of Bryantsev, Diallo, and Goddard.<sup>15</sup> Our second point is that internal correction will give identical  $pK_a$  results to external correction. Our third point is merely an opinion, one we adopted in 2011–2012 when we switched to external correction:<sup>13</sup> using a value for  $G_{aq}(H^+)$  that strays from -270.3 kcal mol<sup>-1</sup> is now tantamount to introducing error into  $G_{aq}(H^+)$  to counter the quantum chemistry model error made on the *other* species ( $BH^+$  and B, or on HA and

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A<sup>-</sup>). It is just as simple, and theoretically more savory (in our opinion), to use external correction.

(15) Bryantsev, V. S.; Diallo, M. S.; Goddard, W. A., III. pK<sub>a</sub> Calculations of Aliphatic Amines, Diamines, and Aminoamides via Density Functional Theory with a Poisson-Boltzmann Continuum Solvent Model. *J. Phys. Chem. A* **2007**, *111*, 4422–4430.

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### Notes

The authors declare no competing financial interest.

## REFERENCES

- (1) Dutra, F. R.; Silva, C. S.; Custodio, R. On the Accuracy of the Direct Method to Calculate pK<sub>a</sub> from Electronic Structure Calculations. *J. Phys. Chem. A* **2021**, *125*, 65–73.
- (2) Lopez, X.; Schaefer, M.; Dejaegere, A.; Karplus, M. Theoretical Evaluation of pK<sub>a</sub> in Phosphoranes: Implications for Phosphate Ester Hydrolysis. *J. Am. Chem. Soc.* **2002**, *124*, 5010–5018.
- (3) Takano, Y.; Houk, K. N. Benchmarking the Conductor-like Polarizable Continuum Model (CPCM) for Aqueous Solvation Free Energies of Neutral and Ionic Organic Molecules. *J. Chem. Theory Comput.* **2005**, *1*, 70–77.
- (4) Coe, J. V. Connecting Cluster Ions and Bulk Aqueous Solvation. A New Determination of Bulk Single Ion Solvation Enthalpies. *Chem. Phys. Lett.* **1994**, *229*, 161–168.
- (5) Tissandier, M. D.; Cowen, K. A.; Feng, W. Y.; Gundlach, E.; Cohen, M. H.; Earhart, A. D.; Coe, J. V.; Tuttle, T. R. The Proton's Absolute Aqueous Enthalpy and Gibbs Free Energy of Solvation from Cluster-Ion Solvation Data. *J. Phys. Chem. A* **1998**, *102*, 7787–7794.
- (6) Coe, J. V. Fundamental Properties of Bulk Water from Cluster Ion Data. *Int. Rev. Phys. Chem.* **2001**, *20*, 33–58.
- (7) Tuttle, T. R., Jr.; Malaxos, S.; Coe, J. V. A New Cluster Pair Method of Determining Absolute Single Ion Solvation Energies Demonstrated in Water and Applied to Ammonia. *J. Phys. Chem. A* **2002**, *106*, 925–932.
- (8) Kelly, C. P.; Cramer, C. J.; Truhlar, D. G. Aqueous Solvation Free Energies of Ions and Ion-Water Clusters Based on an Accurate Value for the Absolute Aqueous Solvation Free Energy of the Proton. *J. Phys. Chem. B* **2006**, *110*, 16066–16081.
- (9) Donald, W. A.; Williams, E. R. An Improved Cluster Pair Correlation Method for Obtaining the Absolute Proton Hydration Energy and Enthalpy Evaluated with an Expanded Data Set. *J. Phys. Chem. B* **2010**, *114*, 13189–13200.
- (10) Camaioni, D. M.; Schwerdtfeger, C. A. Comment on “Accurate Experimental Values for the Free Energies of Hydration of H<sup>+</sup>, OH<sup>-</sup>, and H<sub>3</sub>O<sup>+</sup>”. *J. Phys. Chem. A* **2005**, *109*, 10795–10797.
- (11) Brown, T. N.; Mora-Diez, N. Computational Determination of Aqueous pK<sub>a</sub> Values of Protonated Benzimidazoles (Part 1). *J. Phys. Chem. B* **2006**, *110*, 9270–9279.
- (12) Brown, T. N.; Mora-Diez, N. Computational Determination of Aqueous pK<sub>a</sub> Values of Protonated Benzimidazoles (Part 2). *J. Phys. Chem. B* **2006**, *110*, 20546–20554.
- (13) Sumon, K. Z.; Henni, A.; East, A. L. L. Predicting pK<sub>a</sub> of Amines for CO<sub>2</sub> Capture: Computer versus Pencil-and-Paper. *Ind. Eng. Chem. Res.* **2012**, *51*, 11924–11930.
- (14) Khalili, F.; Henni, A.; East, A. L. L. Entropy Contributions in pK<sub>a</sub> Computation: Application to Alkanolamines and Piperazines. *J. Mol. Struct. THEOCHEM* **2009**, *916*, 1–9.