Comment on "Correlation of aqueous pK$_a$ values of carbon acids with theoretical descriptors: A DFT study"

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In their article, Charif et al. [1] used the B3LYP/6-311++G(d,p) density functional level of theory to estimate gas phase standard state (298.15 K, 1 atm) free energies of acid dissociation ($\Delta_{acid}G^{\circ}_{(g)}$) for 21 carbon acids. These authors then examined correlations between their B3LYP/6-311++G(d,p) $\Delta_{acid}G^{\circ}_{(g)}$ values and corresponding experimental aqueous pK$_a$ measurements. Of the 21 compounds examined by Charif et al. [1], 13 compounds have experimental $\Delta_{acid}G^{\circ}_{(g)}$ in the NIST database [2] (Table 1). The theoretical data in ref. [1] should have been compared with these experimental values in order to assess potential inaccuracies and spurious correlations in the computationally derived dataset. While there is reasonable agreement between the experimental data from ref. [2] and B3LYP/6-311++G(d,p) $\Delta_{acid}G^{\circ}_{(g)}$ from ref. [1] for most compounds, large errors are evident for propanedioic acid, diethyl ester (23.6 kJ/mol), dimedone (23.3 kJ/mol), isopropylidene malonate (14.5 kJ/mol), barbituric acid (44.5 kJ/mol), and toluene (86.7 to 108.7 kJ/mol).

The error between the experimental $\Delta_{acid}G^{\circ}_{(g)}$ and the theoretical value reported by Charif et al. [1] for toluene is striking. In contrast, my B3LYP/6-311++G(d,p) [3–11] calculations using Gaussian 09 [12] obtain a $\Delta_{acid}G^{\circ}_{(g)}$ of 1560.6 kJ/mol for toluene, or 105.1 kJ/mol lower than reported by Charif et al. [1] at the equivalent level of theory. My value is also between and within several kJ/mol for each of the two most recent experimental $\Delta_{acid}G^{\circ}_{(g)}$ measurements of 1557.0±8.4 and 1564.0±8.4 kJ/mol, respectively, and thereby achieves effective chemical accuracy. The discrepancy between my theoretical $\Delta_{acid}G^{\circ}_{(g)}$ value for toluene and that from ref. [1] appears to reside in the molecular free energy for the benzylic anion. My B3LYP/6-311++G(d,p) free energy for the undissociated toluene (-271.540626 hartrees) agrees with the corresponding value reported in the Supplementary Materials by Charif et al. [1] (-271.540629 hartrees), but my free energy of the benzylic anion at this level of theory (-270.936151 hartrees) is substantially lower than that of Charif et al. [1] (-270.896168 hartrees).

When the correct B3LYP/6-311++G(d,p) $\Delta_{acid}G^{\circ}_{(g)}$ value for toluene is included in the correlation between the theoretical $\Delta_{acid}G^{\circ}_{(g)}$ and the experimental aqueous pK$_a$ from ref. [1], toluene is now clearly an outlier (Figure 1(a) [original data from ref. [1]] versus 1(b) [original data from ref. [1] with the exception of a revised $\Delta_{acid}G^{\circ}_{(g)}$=1560.6 kJ/mol for toluene]). Toluene is also an outlier if the experimental $\Delta_{acid}G^{\circ}_{(g)}$ are plotted against the experimental aqueous pK$_a$ for the 13 compounds with available experimental $\Delta_{acid}G^{\circ}_{(g)}$ (Figure 2). Using the B3LYP/6-311++G(d,p) $\Delta_{acid}G^{\circ}_{(g)}$ versus experimental aqueous pK$_a$ regression equation from Charif et al. [1] and the correct B3LYP/6-311++G(d,p) $\Delta_{acid}G^{\circ}_{(g)}$ for toluene yields a predicted pK$_a$ of 30, or 11 units less than the actual pK$_a$. In contrast, the incorrect B3LYP/6-311++G(d,p) $\Delta_{acid}G^{\circ}_{(g)}$ for toluene in Charif et al. [1] gives a predicted pK$_a$ of 41, equivalent to the experimental value. A correct predicted aqueous pK$_a$ for toluene using the B3LYP/6-311++G(d,p) $\Delta_{acid}G^{\circ}_{(g)}$ versus experimental aqueous pK$_a$ regression equation from Charif et al. [1] can only be obtained by using a substantially erroneous B3LYP/6-311++G(d,p) $\Delta_{acid}G^{\circ}_{(g)}$ for this compound.

The findings call into question the generality of the correlation between $\Delta_{acid}G^{\circ}_{(g)}$ and aqueous experimental pK$_a$ values for carbon acids proposed by Charif et al. [1], and also highlight the need for additional studies to investigate what other carbon acid moieties may be outliers. In the present case, either the experimental aqueous pK$_a$ of toluene in the literature is incorrect (and the true value is closer to 30), or the quantitative structure-property relationship proposed in ref. [1] is subject to large outliers that greatly diminish its broad applicability.

References

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Table 1: Comparison between experimental $\Delta_{acid}G^{\circ}_{(g)}$ from ref. [2] and theoretical values at the B3LYP/6-311++G(d,p) level from ref. [1].

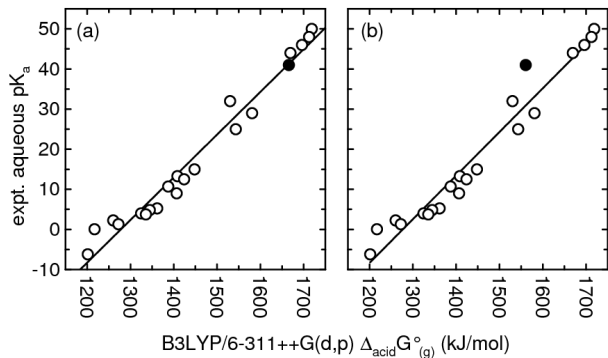| Compound	ID in ref. [1]	B3LYP/6-311++G(d,p) $\Delta_{acid}G^{\circ}_{(g)}$ from ref. [1]	Expt. $\Delta_{acid}G^{\circ}_{(g)}$ from ref. [2]
ethane	1	1718.7	1723.0±8.8
methane	2	1712.3	1709.6±3.3, 1715.0±15.0
cyclopropane	3	1695.9	1708.0±20.0, 1671.0±21.0, 1685.0±8.8
ethylene	4	1669.3	1677.8±2.1, 1670.0±8.8
toluene	5	1665.7	1557.0±8.4, 1564.0±8.4, 1579.0±29.0
trifluoromethane	6	1530.0	1549.0±6.3, 1545.0±8.4
acetylene	8	1543.2	1549.3±1.7, 1547.2±2.5, 1547.2±2.5, 1542.0±8.4, 1576.5±2.5, 1540.0±21.0
cyclopentadiene	9	1447.9	1455.0±8.4, 1459.0±8.4
propanedioic acid, diethyl ester	10	1408.4	1432.0±8.4
acetylacetone	13	1406.5	1409.0±8.4, 1408.0±8.4
dimedone	14	1361.7	1385.0±8.4
isopropylidene malonate	15	1344.5	1359.0
barbituric acid	16	1324.5	1369.0±8.4

Figure 1: Correlation between experimental aqueous pK_a values for various carbon acids from ref. [1] and the corresponding B3LYP/6-311++G(d,p) gas phase standard state (298.15 K, 1 atm) free energies of acid dissociation ($\Delta_{acid}G^{\circ}_{(g)}$) using (a) all data from ref. [1] including the erroneous B3LYP/6-311++G(d,p) $\Delta_{acid}G^{\circ}_{(g)}$ for toluene (filled symbol) and (b) all data from ref. [1] except the current study's corrected B3LYP/6-311++G(d,p) $\Delta_{acid}G^{\circ}_{(g)}$ for toluene (filled symbol). Best fit linear regressions are shown as solid lines.
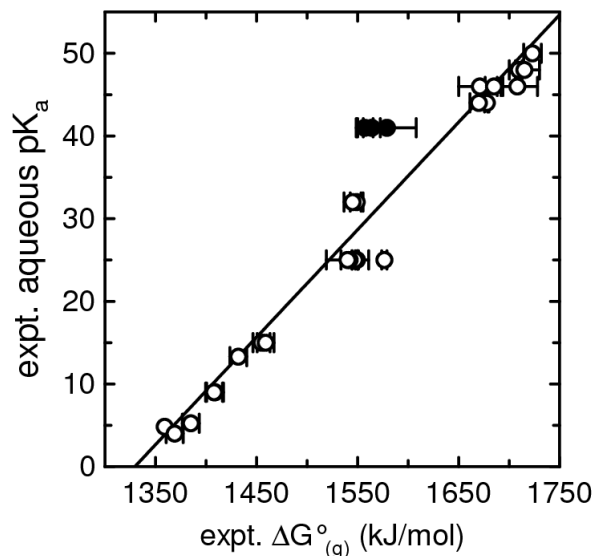

Figure 2: Correlation between experimental aqueous pK_a values for various carbon acids from ref. [1] and the corresponding available experimental gas phase standard state (298.15 K, 1 atm) free energies of acid dissociation ($\Delta_{acid}G^{\circ}_{(g)}$) from ref. [2] as given in Table 1. A best fit linear regression is shown as a solid line. Error bars for the experimental $\Delta_{acid}G^{\circ}_{(g)}$ are taken from ref. [2].

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