A hybrid QM and MM approach for pKa prediction

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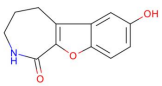
SAMPL6 pKa challenge molecules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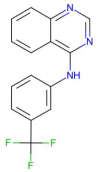
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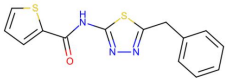
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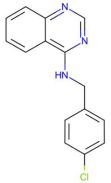
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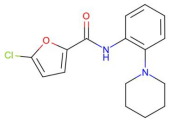
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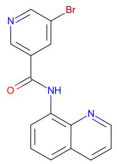
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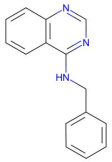
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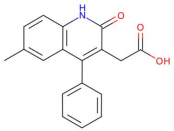
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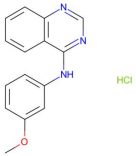
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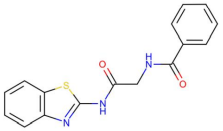
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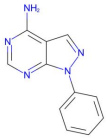
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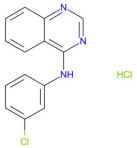
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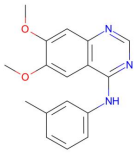
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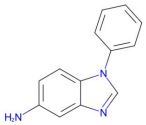
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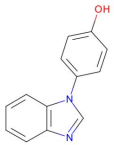
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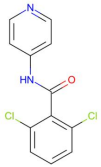
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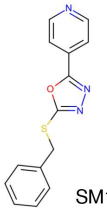
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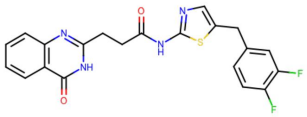
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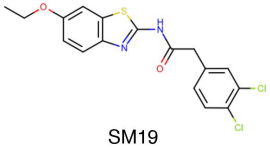
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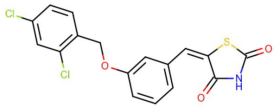
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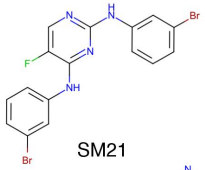
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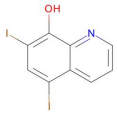
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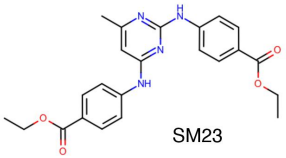
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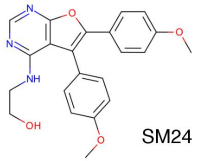
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ΔG and pKa

- For the acid half reaction

$$HA_{aq} \rightarrow H^{+}_{aq} + A^{-}_{aq}$$

- Free energy of protonation is given by

$$\Delta G = G(H^{+}_{aq}) + G(A^{-}_{aq}) - G(HA_{aq})$$

- The pKa value is given by

$$pKa = \Delta G / RTln10$$

Born-Haber cycle for deprotonation

$$
\begin{tikzcd}
HA_{(g)} \arrow[r, "\Delta G_{(g),deprot}"] \arrow[d, "\Delta G_{solv}(HA)", "\text{SMD}"'] & A^-_{(g)} \arrow[d, "\Delta G_{solv}(A^-)", "\text{SMD}"'] & + & H^+_{(g)} \arrow[d, "\Delta G^{exp}_{solv}(H^+)"] \\
HA_{(aq)} \arrow[r, "\Delta G_{(aq),deprot}"] & A^-_{(aq)} & + & H^+_{(aq)}
\end{tikzcd}
$$

Explicit solvent

$$
\begin{tikzcd}
HA_{(g)} \arrow[r, "\Delta G^{QM}_{(g),deprot}"] \arrow[d, "\Delta G^{MM}_{solv}(HA)", "\text{Explicit Solv}"'] & A^-_{(g)} \quad + \quad H^+_{(g)} \arrow[d, "\Delta G^{MM}_{solv}(A^-)", "\text{Explicit Solv}"'] \arrow[d, "\Delta G^{exp}_{solv}(H^+)"] \\
HA_{(aq)} \arrow[r, "\Delta G_{(aq),deprot}"] & A^-_{(aq)} \quad + \quad H^+_{(aq)}
\end{tikzcd}
$$

Alchemical free energy difference

$$
\begin{tikzcd}
HA_{(g)} \arrow[r, "\Delta G^{FEP}_{(g)}"] \arrow[d, "\Delta G^{MM}_{solv}(HA)", "\text{Explicit Solv}"'] & A^-_{(g)} \arrow[d, "\Delta G^{MM}_{solv}(A^-)", "\text{Explicit Solv}"'] \\
HA_{(aq)} \arrow[r, "\Delta G^{FEP}_{(aq)}"] & A^-_{(aq)}
\end{tikzcd}
$$

$$\Delta G^{solv}_{A^-} - \Delta G^{solv}_{HA} = \Delta G^{FEP}_{aq} - \Delta G^{FEP}_{g}$$

Hybrid QM and MM approach

From the thermodynamic cycle at the QM level

$$\Delta G_{aq} = \Delta G_g^{QM} + \Delta G_{H+}^{solv} + (\Delta G_{A-}^{solv} - \Delta G_{HA}^{solv})$$

From the acid half reaction,

$$\Delta G_{A-}^{solv} - \Delta G_{HA}^{solv} = \Delta G_{aq}^{FEP} - \Delta G_g^{FEP}$$

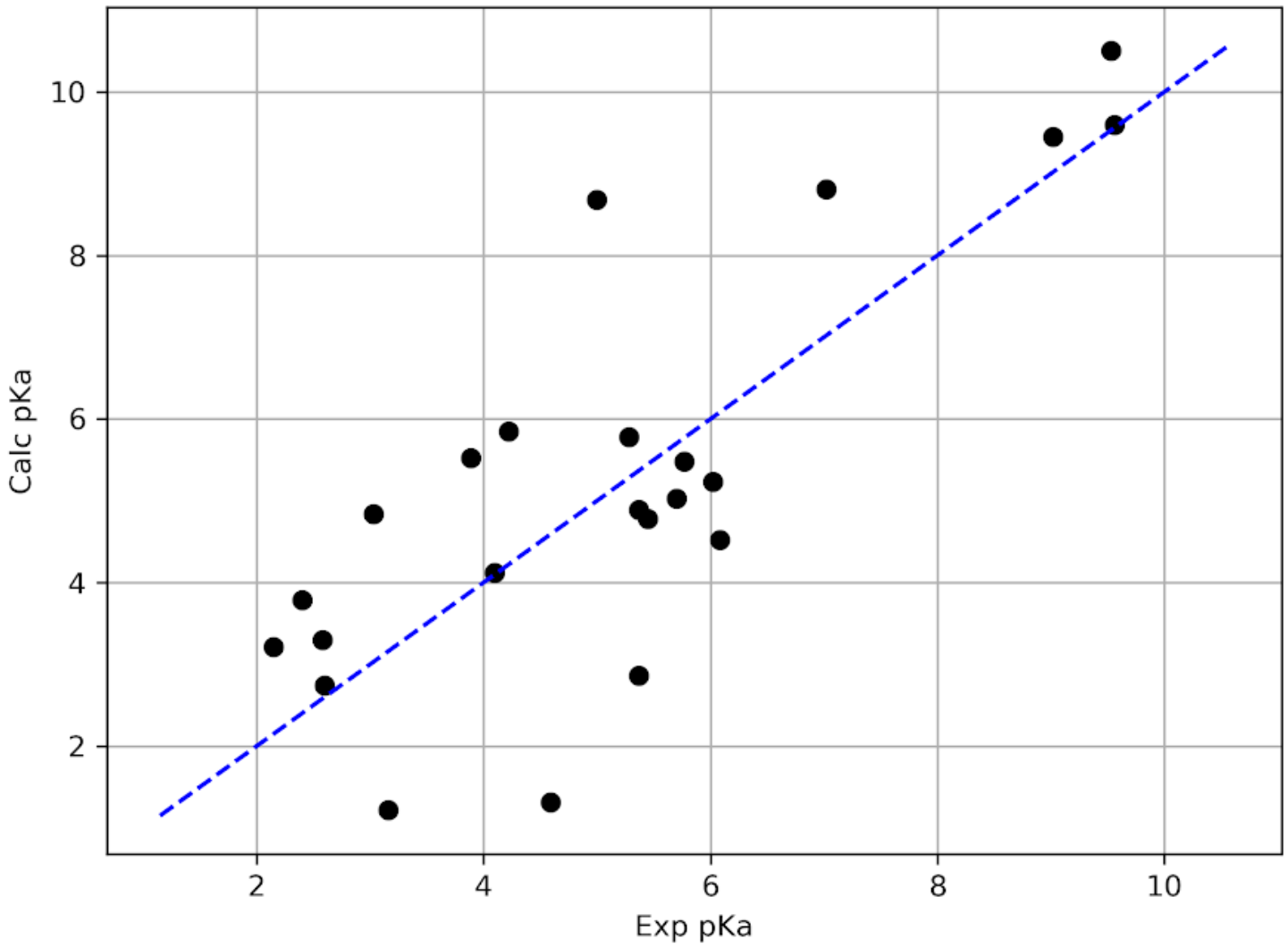
Combining the two,

$$\Delta G_{aq} = \Delta G_g^{QM} + \Delta G_{H+}^{solv} + (\Delta G_{aq}^{FEP} - \Delta G_g^{FEP})$$

Protocol

- Each microstate optimized at M062X/6-31G* level of theory using Gaussian-16
- Parameterization done at MP2/6-31G* using Antechamber.
- Thermodynamic integration performed in the gas and aqueous phases to obtain the solvation free energy difference between the protonated and deprotonated pair

Results



RMSE : 1.80 pKa

$r^2 = 0.79$

Limitations of the approach

- Experimental value for the solvation free energy of proton
- Compatibility of the force field parameters with the chosen level of theory
- proton van der waals probably interfering with proper local coordination with solvent
- Errors associated with non-global minima for the gas phase quantum ΔG calculation

Further improvements

- Force matching with a higher level quantum level theory to improve the parameters
- Polarizable force field
- Switching off the van der waals interactions of the proton as well

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