Supporting Information for:
“Testing a heterogeneous polarizable continuum model against exact Poisson boundary conditions”

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S1 Details of the Voronoi Construction

PEqS requires a dense three-dimensional grid with $\varepsilon(\mathbf{r})$ defined at every point. In this section, we describe the use of "fuzzy" Voronoi cells, otherwise known as Becke weights,[2] to construct permittivity functions $\varepsilon(\mathbf{r})$ that map onto a model in which individual atoms are assigned one of two dielectric constants, either $\varepsilon_{\text{nonp}}$ or $\varepsilon_{\text{solv}}$.

For the model environments considered here, where the dielectric constant is defined atomwise, this requires smooth interpolation between different atomic values of the dielectric constant (ε_A in eq. 28). values of ε. For this we use Becke's version of Voronoi cells with smooth boundaries.[2] This scheme was developed by Becke for numerical evaluation of three-dimensional integrals,

$$\int F(\mathbf{r})\, d\mathbf{r} \approx \sum_i w_i F(\mathbf{r}_i) \;, \tag{S1}$$

where $\{\mathbf{r}_i\}$ and $\{w_i\}$ are a set of quadrature points and weights, respectively. For molecular integrals, it makes sense to partition the sum in eq. S1 into atomic regions and to use nuclear-centered grids for each region. The partition is accomplished using Voronoi polyhedra,[3] defined by the nuclei.

The idea is to define a weight function $w_A(\mathbf{r})$ for each atom A, such that the normalization condition

$$\sum_A w_A(\mathbf{r}) = 1 \tag{S2}$$

holds at every point $\mathbf{r}$ in three-dimensional space. This condition implies that the integrand in eq. (S1) can be decomposed into atomic contributions,

$$F(\mathbf{r}) = \sum_A F_A(\mathbf{r}) \;, \tag{S3}$$

each given by

$$F_A(\mathbf{r}) = w_A(\mathbf{r})\, F(\mathbf{r}) \;, \tag{S4}$$

with $F_A(\mathbf{r})$ to be integrated by using a grid that is centered on nucleus A. The weight function $w_A(\mathbf{r})$ should have limits

$$\begin{aligned} w_A(\mathbf{r}) &\to 1, \qquad \text{as } \|\mathbf{r} - \mathbf{R}_A\| \to 0 \\ wA(\mathbf{r}) &\to 0, \qquad \text{as } \|\mathbf{r} - \mathbf{R}_A\| \to \infty \;, \end{aligned} \tag{S5}$$

and should be well-behaved enough so that the quadrature subject to discontinuous jumps as the nuclei are displaced. In the present context, this allows for smooth interpolation between an atomwise definition of $\varepsilon(\mathbf{r})$, as in eq. 28.

Following Becke,[2] we define the Voronoi polyhedra using a two-center coordinate system, via confocal elliptical coordinates $\mathbf{r} = (\lambda_{AB}, \mu_{AB}, \phi_{AB})$ for the pair of nuclei situated at $\mathbf{R}_A$ and $\mathbf{R}_B$. In this coordinate system, ϕ_{AB} is the angle between $\mathbf{r}$ and the internuclear axis $\mathbf{R}_A - \mathbf{R}_B$. The other two coordinates are

$$\lambda_{AB} = \frac{r_A + r_B}{R_{AB}} \tag{S6}$$

and

$$\mu_{AB} = \frac{r_A - r_B}{R_{AB}} \tag{S7}$$

where $r_A = \|\mathbf{r} - \mathbf{R}_A\|$, $r_B = \|\mathbf{r} - \mathbf{R}_B\|$, and $R_{AB} = \|\mathbf{R}_A - \mathbf{R}_B\|$. Note that

$$-1 \le \mu_{AB} \le 1 \;. \tag{S8}$$

One may use this coordinate to define a step function

$$\delta(\mu_{AB}) = \begin{cases} 1, & -1 \leq \mu_{AB} \leq 0 \\ 0, & 0 < \mu_{AB} \leq 1 \end{cases} . \tag{S9}$$

Using the fact the surface defined by $\mu_{AB} \equiv 0$ is the perpendicular bisector of $\mathbf{R}_A - \mathbf{R}_B$,[2] one may define the Voronoi polyhedron for nucleus A as

$$P_A(\mathbf{r}) = \prod_{B \neq A} \delta(\mu_{AB}) . \tag{S10}$$

This polyhedron has sharp boundaries. Specifically, $P_A(\mathbf{r}) = 1$ if $\mathbf{R}_A$ is the closest nucleus to the point $\mathbf{r}$, and $P_A(\mathbf{r}) = 0$ otherwise.

To obtain a weight function that is continuous and smooth, we must introduce switching functions. In other words, there is a discontinuity at $\mu_{AB} = 0$ that needs to be resolved in order to obtain "fuzzy" Voronoi polyhedra. Again following Becke,[2] we use

$$\delta(\mu) = [1 - g_k(\mu)]/2 \tag{S11}$$

to replace the function defined in eq. S9, where $g_k(\mu)$ is defined by recursive application of a polynomial

$$p(\mu) = \frac{3}{2}\mu - \frac{1}{2}\mu^3 . \tag{S12}$$

For example,

$$\begin{aligned} g_1(\mu) &= p(\mu) \\ g_2(\mu) &= p(p(\mu)) \\ g_3(\mu) &= p(p(p(\mu))) . \end{aligned} \tag{S13}$$

Smaller values of k in eq. S11 lead to slower switching, with sharper switching as $k \to \infty$.[2] On the basis of convergence tests presented in Table S2, the value $k = 10$ was selected for use in the present work.

This recursive definition of $\delta(\mu)$ is used to weight the grid points within each Voronoi cell, according to the function $P_A(\mathbf{r})$ in eq. S10. Normalizing the weights leads us to define

$$w_A(\mathbf{r}) = \frac{P_A(\mathbf{r})}{\sum_B P_B(\mathbf{r})} . \tag{S14}$$

Then $w_A(\mathbf{r}) \approx 1$ if $\mathbf{r}$ is close to $\mathbf{R}_A$, whereas $w_A(\mathbf{r}) \to 0$ as $\mathbf{r} \to \mathbf{R}_B$ (for $B \neq A$), consistent with the limits in eq. S5.

S2 Numerical Convergence Tests

Table S1: Solvation energies ΔG_{elst} as a function of the grid spacing.[a]

Molecule	ΔG_{elst} (kcal/mol)				
	0.29 Å	0.20 Å	0.15 Å	0.10 Å	0.05 Å
NO_3^-	−61.4	−63.6	−63.6	−63.6	−63.6
NH_4^+	−47.0	−79.5	−79.3	−79.3	−79.2
NaCl	−23.0	−23.2	−23.1	−23.1	−23.0
$CHOO^-$	−68.2	−68.6	−68.6	−68.6	−68.5
H_3O^+	−84.2	−75.5	−75.5	−87.6	−87.5

[a] All grids are cubic ($\Delta x = \Delta y = \Delta z$) and extend to 10 Å. Calculations were performed at the HF/STO-3G level.

Table S2: Solvation energies as a function of the k parameter in the Becke weight function (eq. S11).[a]

Solute	Scheme[b]	ΔG_{elst} (kcal/mol)			
		$k = 3$	$k = 7$	$k = 10$	$k = 15$
NO_3^-	1	−42.5	−38.7	−37.7	−37.7
NO_3^-	2	−57.8	−55.7	−55.1	−55.1
NaCl	1	−11.9	−7.8	−7.5	−7.5
NaCl	2	−15.9	−13.7	−13.5	−13.5
$CHOO^-$	1	−53.4	−50.5	−49.7	−49.7
$CHOO^-$	2	−67.1	−66.7	−66.5	−66.5
NH_4^+	1	−50.3	−44.6	−43.0	−43.4
NH_4^+	2	−68.5	−64.2	−63.2	−63.2
H_3O^+	1	−61.4	−55.4	−54.0	−54.1
H_3O^+	2	−80.6	−77.5	−76.7	−76.7

[a] All grids extend to 8 Å and calculations were performed at the HF/STO-3G level. [b] As defined in Fig. 3.

S3 Basis Set Dependence

S3.1 Hartree-Fock Calculations

Table S3: Voronoi-PEqS solvation energies computed using Hartree-Fock theory in various basis sets, using $\varepsilon_{\mathrm{solv}} = 78.4$ and $\varepsilon_{\mathrm{nonp}} = 1$.[a]

Solute	Scheme[b]	ΔG_{elst} (kcal/mol)				
		STO-3G	def2-SVP	def2-SVPD	def2-TZVP	def2-TZVPD
NO_3^-	1	−38.2	−38.9	−39.7	−39.6	−39.8
NO_3^-	2	−55.6	−55.8	−55.4	−55.8	−55.5
NaCl	1	−7.7	−7.3	−8.0	−7.6	−7.7
NaCl	2	−13.7	−11.3	−11.8	−11.7	−11.5
$CHOO^-$	1	−50.3	−57.1	−58.2	−58.3	−58.2
$CHOO^-$	2	−67.1	−73.7	−73.3	−73.8	−73.2
NH_4^+	1	−44.0	−44.7	−45.3	−45.0	−45.3
NH_4^+	2	−63.9	−64.0	−64.3	−64.2	−64.3
H_3O^+	1	−54.9	−54.4	−54.7	−54.6	−54.6
H_3O^+	2	−77.6	−76.8	−76.9	−77.0	−76.8
Glycine	1	−1.8	−3.0	−3.1	−3.1	−3.1
Glycine	2	−2.7	−4.2	−4.6	−4.6	−4.6
Benzene	1	−0.2	−0.9	−1.0	−1.0	−1.0
Benzene	2	−0.5	−2.0	−2.2	−2.2	−2.2
Phenol	1	−2.3	−4.0	−4.1	−4.1	−4.0
Phenol	2	−2.8	−5.6	−5.9	−5.8	−5.7

[a] All calculations use an 8 Å total grid size with $k = 10$, $L = 0.5$ Å, and $\Delta x = \Delta y = \Delta z = 0.05$ Å.
[b] As defined in Fig. 3.

Table S4: Voronoi-PEqS solvation energies computed using Hartree-Fock theory in various basis sets, using $\varepsilon_{\mathrm{solv}} = 78.4$ and $\varepsilon_{\mathrm{nonp}} = 2$.[a]

Solute	Scheme[b]	ΔG_{elst} (kcal/mol)				
		STO-3G	def2-SVP	def2-SVPD	def2-TZVP	def2-TZVPD
NO_3^-	1	−49.0	−49.2	−49.0	−49.3	−49.1
NO_3^-	2	−59.0	−59.0	−58.3	−58.8	−58.4
NaCl	1	−13.8	−12.4	−13.5	−13.1	−13.2
NaCl	2	−17.3	−14.9	−15.7	−15.5	−15.4
$CHOO^-$	1	−58.2	−63.9	−64.3	−64.6	−64.3
$CHOO^-$	2	−68.2	−74.3	−73.9	−74.4	−73.8
NH_4^+	1	−58.4	−58.5	−58.8	−58.7	−58.8
NH_4^+	2	−69.8	−69.7	−69.9	−69.8	−69.9
H_3O^+	1	−67.9	−67.3	−67.4	−67.4	−67.3
H_3O^+	2	−81.6	−80.9	−81.0	−81.1	−80.9
Glycine	1	−3.0	−5.1	−5.3	−5.3	−5.3
Glycine	2	−3.6	−6.0	−6.5	−6.4	−6.4
Benzene	1	−0.4	−1.5	−1.6	−1.6	−1.6
Benzene	2	−0.6	−2.3	−2.5	−2.6	−2.5
Phenol	1	−2.5	−4.7	−4.8	−4.8	−4.7
Phenol	2	−2.8	−5.9	−6.2	−6.2	−6.0

[a] All calculations use an 8 Å total grid size with $k = 10$, $L = 0.5$ Å, and $\Delta x = \Delta y = \Delta z = 0.05$ Å.

[b] As defined in Fig. 3.

Table S5: Voronoi-PEqS solvation energies computed using Hartree-Fock theory in various basis sets, using $\varepsilon_{\mathrm{solv}} = 78.4$ and $\varepsilon_{\mathrm{nonp}} = 4$.[a]

Solute	Scheme[b]	ΔG_{elst} (kcal/mol)				
		STO-3G	def2-SVP	def2-SVPD	def2-TZVP	def2-TZVPD
NO_3^-	1	−55.4	−55.4	−54.7	−55.2	−54.8
NO_3^-	2	−61.0	−61.0	−60.0	−60.6	−60.1
NaCl	1	−17.6	−15.8	−17.1	−16.7	−16.8
NaCl	2	−19.5	−17.2	−18.2	−17.9	−17.9
$CHOO^-$	1	−62.8	−68.0	−68.0	−68.4	−67.9
$CHOO^-$	2	−68.6	−74.3	−74.0	−74.4	−73.9
NH_4^+	1	−67.2	−67.0	−67.2	−67.2	−67.2
NH_4^+	2	−73.5	−73.3	−73.4	−73.4	−73.4
H_3O^+	1	−76.0	−75.3	−75.4	−75.5	−75.3
H_3O^+	2	−84.0	−83.4	−83.5	−83.6	−83.4
Glycine	1	−3.9	−6.9	−7.2	−7.2	−7.14
Glycine	2	−4.3	−7.4	−8.0	−7.9	−7.95
Benzene	1	−0.5	−2.0	−2.2	−2.2	−2.10
Benzene	2	−0.6	−2.6	−2.8	−2.9	−2.77
Phenol	1	−2.6	−5.3	−5.5	−5.5	−5.37
Phenol	2	−2.9	−6.2	−6.5	−6.5	−6.33

[a] All calculations use an 8 Å total grid size with $k = 10$, $L = 0.5$ Å, and $\Delta x = \Delta y = \Delta z = 0.05$ Å.

[b] As defined in Fig. 3.

Table S6: Voronoi-PEqS solvation energies computed using Hartree-Fock theory in various basis sets, using $\varepsilon_{\text{solv}} = 78.4$ and $\varepsilon_{\text{nonp}} = 10$.[a]

Solute	Scheme[b]	ΔG_{elst} (kcal/mol)				
		STO-3G	def2-SVP	def2-SVPD	def2-TZVP	def2-TZVPD
NO_3^-	1	−60.1	−60.1	−59.1	−59.7	−59.2
NO_3^-	2	−62.6	−62.6	−61.5	−62.1	−61.6
NaCl	1	−20.5	−18.5	−20.0	−19.6	−19.6
NaCl	2	−21.3	−19.1	−20.4	−20.0	−20.0
$CHOO^-$	1	−66.2	−71.3	−71.1	−71.5	−71.0
$CHOO^-$	2	−69.0	−74.4	−74.0	−74.5	−74.0
NH_4^+	1	−73.9	−73.7	−73.8	−73.8	−73.8
NH_4^+	2	−76.7	−76.4	−76.6	−76.6	−76.6
H_3O^+	1	−82.4	−81.8	−81.9	−82.0	−81.8
H_3O^+	2	−86.2	−85.6	−85.7	−85.8	−85.6
Glycine	1	−4.8	−8.6	−9.2	−9.1	−9.1
Glycine	2	−5.0	−8.9	−9.6	−9.4	−9.5
Benzene	1	−0.6	−2.5	−2.8	−2.8	−2.7
Benzene	2	−0.7	−2.8	−3.2	−3.2	−3.1
Phenol	1	−2.8	−6.0	−6.3	−6.3	−6.1
Phenol	2	−3.0	−6.5	−6.8	−6.8	−6.6

[a] All calculations use an 8 Å total grid size with $k = 10$, $L = 0.5$ Å, and $\Delta x = \Delta y = \Delta z = 0.05$ Å.

[b] As defined in Fig. 3.

Table S7: HetPCM solvation energies computed using Hartree-Fock theory in various basis sets, using $\varepsilon_{\text{solv}} = 78.4$ and $\varepsilon_{\text{nonp}} = 1$.

Solute	Scheme[a]	ΔG_{elst} (kcal/mol)				
		STO-3G	def2-SVP	def2-SVPD	def2-TZVP	def2-TZVPD
NO_3^-	1	−23.2	−25.3	−25.5	−25.4	−25.5
NO_3^-	2	−44.2	−46.9	−46.6	−46.7	−46.6
NaCl	1	−9.4	−9.0	−9.7	−9.3	−9.4
NaCl	2	−14.5	−11.8	−12.2	−12.1	−11.9
$CHOO^-$	1	−34.6	−44.1	−46.2	−45.6	−45.9
$CHOO^-$	2	−58.3	−70.9	−71.7	−71.4	−71.2
NH_4^+	1	−14.5	−14.8	−15.0	−15.1	−15.2
NH_4^+	2	−28.4	−28.7	−29.0	−29.4	−29.4
H_3O^+	1	−20.6	−21.2	−21.3	−21.4	−21.4
H_3O^+	2	−40.2	−41.2	−41.5	−41.7	−41.6
Glycine	1	−1.9	−3.1	−3.3	−3.2	−3.1
Glycine	2	−2.6	−3.6	−3.8	−3.9	−3.6
Benzene	1	−0.1	−0.5	−0.6	−0.6	−0.5
Benzene	2	−0.4	−1.6	−1.8	−1.8	−1.6
Phenol	1	−1.1	−1.8	−1.8	−1.8	−1.8
Phenol	2	−1.7	−3.4	−3.5	−3.4	−3.4

[a] As defined in Fig. 3.

Table S8: HetPCM solvation energies computed using Hartree-Fock theory in various basis sets, using $\varepsilon_{\mathrm{solv}} = 78.4$ and $\varepsilon_{\mathrm{nonp}} = 2$.

Solute	Scheme[a]	ΔG_{elst} (kcal/mol)				
		STO-3G	def2-SVP	def2-SVPD	def2-TZVP	def2-TZVPD
NO_3^-	1	−43.9	−44.5	−43.8	−44.1	−43.8
NO_3^-	2	−54.2	−55.2	−54.4	−54.7	−54.3
NaCl	1	−16.9	−15.3	−16.3	−15.9	−15.9
NaCl	2	−19.5	−17.0	−18.0	−17.6	−17.6
$CHOO^-$	1	−52.2	−59.3	−59.8	−59.8	−59.6
$CHOO^-$	2	−64.3	−73.4	−73.6	−73.6	−73.2
NH_4^+	1	−48.1	−48.0	−48.2	−48.3	−48.3
NH_4^+	2	−54.9	−54.8	−55.0	−55.2	−55.2
H_3O^+	1	−55.7	−55.5	−55.6	−55.8	−55.6
H_3O^+	2	−65.3	−65.5	−65.6	−65.9	−65.7
Glycine	1	−4.0	−6.8	−7.0	−7.0	−6.8
Glycine	2	−4.4	−7.2	−7.6	−7.6	−7.2
Benzene	1	−0.5	−1.8	−2.0	−2.0	−1.8
Benzene	2	−0.6	−2.4	−2.7	−2.7	−2.4
Phenol	1	−1.6	−3.4	−3.5	−3.5	−3.4
Phenol	2	−1.9	−4.3	−4.5	−4.4	−4.3

[a] As defined in Fig. 3.

Table S9: HetPCM solvation energies computed using Hartree-Fock theory in various basis sets, using $\varepsilon_{\mathrm{solv}} = 78.4$ and $\varepsilon_{\mathrm{nonp}} = 4$.

Solute	Scheme[a]	ΔG_{elst} (kcal/mol)				
		STO-3G	def2-SVP	def2-SVPD	def2-TZVP	def2-TZVPD
NO_3^-	1	−54.6	−54.8	−53.8	−54.2	−53.7
NO_3^-	2	−59.7	−60.0	−58.9	−59.3	−58.8
NaCl	1	−20.8	−18.8	−20.0	−19.6	−19.6
NaCl	2	−22.1	−19.7	−20.9	−20.5	−20.5
$CHOO^-$	1	−61.4	−67.5	−67.5	−67.7	−67.3
$CHOO^-$	2	−67.3	−74.6	−74.5	−74.8	−74.2
NH_4^+	1	−65.1	−64.9	−65.0	−65.1	−65.1
NH_4^+	2	−68.4	−68.1	−68.3	−68.5	−68.5
H_3O^+	1	−73.4	−73.0	−73.1	−73.3	−73.1
H_3O^+	2	−78.1	−77.9	−78.0	−78.2	−78.0
Glycine	1	−5.1	−9.1	−9.5	−9.4	−9.1
Glycine	2	−5.3	−9.4	−9.9	−9.8	−9.4
Benzene	1	−0.7	−2.6	−2.8	−2.9	−2.6
Benzene	2	−0.8	−2.9	−3.2	−3.2	−2.9
Phenol	1	−1.9	−4.4	−4.6	−4.5	−4.4
Phenol	2	−2.1	−4.8	−5.0	−5.0	−4.8

[a] As defined in Fig. 3.

Table S10: HetPCM solvation energies computed using Hartree-Fock theory in various basis sets, using $\varepsilon_{\text{solv}} = 78.4$ and $\varepsilon_{\text{nonp}} = 10$.

Solute	Scheme[a]	ΔG_{elst} (kcal/mol)				
		STO-3G	def2-SVP	def2-SVPD	def2-TZVP	def2-TZVPD
NO_3^-	1	−61.2	−61.2	−60.0	−60.5	−60.0
NO_3^-	2	−63.0	−63.1	−61.9	−62.4	−61.8
NaCl	1	−23.2	−21.0	−22.4	−21.9	−21.9
NaCl	2	−23.6	−21.4	−22.8	−22.3	−22.3
$CHOO^-$	1	−67.0	−72.7	−72.4	−72.8	−72.2
$CHOO^-$	2	−69.2	−75.3	−75.1	−75.4	−74.8
NH_4^+	1	−75.4	−75.0	−75.2	−75.3	−75.3
NH_4^+	2	−76.6	−76.2	−76.4	−76.6	−76.6
H_3O^+	1	−84.1	−83.6	−83.7	−83.9	−83.6
H_3O^+	2	−85.8	−85.4	−85.5	−85.7	−85.5
Glycine	1	−5.9	−10.6	−11.3	−11.1	−11.1
Glycine	2	−5.9	−10.7	−11.4	−11.3	−11.3
Benzene	1	−0.8	−3.1	−3.4	−3.4	−3.3
Benzene	2	−0.8	−3.2	−3.5	−3.6	−3.4
Phenol	1	−2.1	−5.0	−5.2	−5.2	−5.0
Phenol	2	−2.1	−5.2	−5.4	−5.4	−5.2

[a] As defined in Fig. 3.

S3.2 ωB97M-V Calculations

Table S11: Voronoi-PEqS solvation energies computed using ωB97M-V in various basis sets, using $\varepsilon_{\text{solv}} = 78.4$ and $\varepsilon_{\text{nonp}} = 1$.[a]

Solute	Scheme[b]	ΔG_{elst} (kcal/mol)			
		def2-SVP	def2-SVPD	def2-TZVP	def2-TZVPD
NO_3^-	1	−39.4	−40.0	−40.2	−40.2
NO_3^-	2	−56.0	−55.0	−56.0	−55.2
NaCl	1	−6.6	−7.6	−7.1	−7.3
NaCl	2	−9.7	−10.6	−10.5	−10.4
$CHOO^-$	1	−54.6	−56.5	−56.7	−56.6
$CHOO^-$	2	−70.4	−70.5	−71.3	−70.4
NH_4^+	1	−45.0	−45.7	−45.2	−45.6
NH_4^+	2	−64.2	−64.6	−64.4	−64.5
H_3O^+	1	−54.4	−54.9	−54.6	−54.7
H_3O^+	2	−76.6	−76.9	−76.9	−76.8
Glycine	1	−2.7	−3.0	−3.0	−3.0
Glycine	2	−3.8	−4.4	−4.4	−4.4
Benzene	1	−0.7	−0.8	−0.8	−0.8
Benzene	2	−1.6	−1.8	−1.9	−1.8
Phenol	1	−3.5	−3.8	−3.8	−3.7
Phenol	2	−4.9	−5.3	−5.4	−5.2

[a] All calculations use an 8 Å total grid size with $k = 10$, $L = 0.5$ Å, and $\Delta x = \Delta y = \Delta z = 0.05$ Å. [b] As defined in Fig. 3.

Table S12: Voronoi-PEqS solvation energies computed using ωB97M-V in various basis sets, using $\varepsilon_{\text{solv}} = 78.4$ and $\varepsilon_{\text{nonp}} = 2$.[a]

Solute	Scheme[b]	ΔG_{elst} (kcal/mol)			
		def2-SVP	def2-SVPD	def2-TZVP	def2-TZVPD
NO_3^-	1	−49.2	−49.0	−49.3	−49.1
NO_3^-	2	−59.0	−58.3	−58.8	−58.4
NaCl	1	−12.4	−13.5	−13.1	−13.2
NaCl	2	−14.9	−15.7	−15.5	−15.4
$CHOO^-$	1	−63.9	−64.3	−64.6	−64.2
$CHOO^-$	2	−74.3	−73.9	−74.4	−73.8
NH_4^+	1	−58.5	−58.8	−58.7	−58.8
NH_4^+	2	−69.7	−69.9	−69.8	−69.9
H_3O^+	1	−67.3	−67.4	−67.4	−67.3
H_3O^+	2	−80.9	−81.0	−81.1	−80.9
Glycine	1	−4.4	−4.9	−4.9	−4.9
Glycine	2	−5.2	−6.0	−6.0	−6.0
Benzene	1	−1.2	−1.3	−1.4	−1.3
Benzene	2	−1.8	−2.1	−2.2	−2.1
Phenol	1	−4.1	−4.4	−4.4	−4.3
Phenol	2	−5.2	−5.6	−5.7	−5.5

[a] All calculations use an 8 Å total grid size with $k = 10$, $L = 0.5$ Å, and $\Delta x = \Delta y = \Delta z = 0.05$ Å. [b] As defined in Fig. 3.

Table S13: Voronoi-PEqS solvation energies computed using ωB97M-V in various basis sets, using $\varepsilon_{\text{solv}} = 78.4$ and $\varepsilon_{\text{nonp}} = 4$.[a]

Solute	Scheme[b]	ΔG_{elst} (kcal/mol)			
		def2-SVP	def2-SVPD	def2-TZVP	def2-TZVPD
NO_3^-	1	−55.4	−54.7	−55.2	−54.8
NO_3^-	2	−61.0	−60.0	−60.6	−60.1
NaCl	1	−15.8	−17.1	−16.7	−16.8
NaCl	2	−17.2	−18.2	−17.9	−17.9
$CHOO^-$	1	−68.0	−68.0	−68.4	−67.9
$CHOO^-$	2	−74.3	−74.0	−74.4	−73.9
NH_4^+	1	−67.0	−67.2	−67.2	−67.2
NH_4^+	2	−73.3	−73.4	−73.4	−73.4
H_3O^+	1	−75.3	−75.4	−75.5	−75.3
H_3O^+	2	−83.4	−83.5	−83.6	−83.4
Glycine	1	−5.8	−6.6	−6.6	−6.5
Glycine	2	−6.4	−7.4	−7.3	−7.3
Benzene	1	−1.6	−1.8	−1.8	−1.8
Benzene	2	−2.0	−2.4	−2.5	−2.4
Phenol	1	−4.6	−5.0	−5.0	−4.9
Phenol	2	−5.4	−5.8	−5.9	−5.8

[a] All calculations use an 8 Å total grid size with $k = 10$, $L = 0.5$ Å, and $\Delta x = \Delta y = \Delta z = 0.05$ Å. [b] As defined in Fig. 3.

Table S14: Voronoi-PEqS solvation energies computed using ωB97M-V various basis sets, using $\varepsilon_{\text{solv}} = 78.4$ and $\varepsilon_{\text{nonp}} = 10$.[a]

Solute	Scheme[b]	ΔG_{elst} (kcal/mol)			
		def2-SVP	def2-SVPD	def2-TZVP	def2-TZVPD
NO_3^-	1	−60.1	−59.1	−59.7	−59.2
NO_3^-	2	−62.6	−61.5	−62.1	−61.6
NaCl	1	−18.5	−20.0	−19.6	−19.6
NaCl	2	−19.1	−20.4	−20.0	−20.0
$CHOO^-$	1	−71.3	−71.1	−71.5	−71.0
$CHOO^-$	2	−74.4	−74.0	−74.5	−74.0
NH_4^+	1	−73.7	−73.8	−73.8	−73.8
NH_4^+	2	−76.4	−76.6	−76.6	−76.6
H_3O^+	1	−81.8	−81.9	−82.0	−81.8
H_3O^+	2	−85.6	−85.7	−85.8	−85.6
Glycine	1	−7.3	−8.4	−8.2	−8.3
Glycine	2	−7.5	−8.8	−8.6	−8.7
Benzene	1	−2.0	−2.3	−2.4	−2.3
Benzene	2	−2.3	−2.6	−2.8	−2.7
Phenol	1	−5.2	−5.6	−5.7	−5.5
Phenol	2	−5.6	−6.1	−6.2	−6.0

[a] All calculations use an 8 Å total grid size with $k = 10$, $L = 0.5$ Å, and $\Delta x = \Delta y = \Delta z = 0.05$ Å. [b] As defined in Fig. 3.

Table S15: HetPCM solvation energies computed using ωB97M-V in various basis sets, using $\varepsilon_{\text{solv}} = 78.4$ and $\varepsilon_{\text{nonp}} = 1$.

Solute	Scheme[a]	ΔG_{elst} (kcal/mol)			
		def2-SVP	def2-SVPD	def2-TZVP	def2-TZVPD
NO_3^-	1	−25.0	−25.4	−25.6	−25.5
NO_3^-	2	−46.3	−46.1	−46.5	−46.2
NaCl	1	−8.1	−9.2	−8.7	−8.9
NaCl	2	−10.1	−11.0	−10.9	−10.8
$CHOO^-$	1	−40.0	−43.7	−43.0	−43.6
$CHOO^-$	2	−64.9	−67.3	−67.1	−67.0
NH_4^+	1	−14.6	−14.9	−15.1	−15.1
NH_4^+	2	−28.4	−28.9	−29.3	−29.4
H_3O^+	1	−20.8	−21.0	−21.2	−21.1
H_3O^+	2	−40.4	−40.9	−41.2	−41.1
Glycine	1	−2.9	−3.2	−3.2	−3.1
Glycine	2	−3.3	−3.7	−3.8	−3.8
Benzene	1	−0.4	−0.5	−0.5	−0.5
Benzene	2	−1.3	−1.5	−1.5	−1.5
Phenol	1	−1.4	−1.6	−1.5	−1.5
Phenol	2	−2.8	−3.0	−3.0	−2.9

[a] As defined in Fig. 3.

Table S16: HetPCM solvation energies computed using ωB97M-V theory in various basis sets, using $\varepsilon_{\text{solv}} = 78.4$ and $\varepsilon_{\text{nonp}} = 2$.

Solute	Scheme[a]	ΔG_{elst} (kcal/mol)			
		def2-SVP	def2-SVPD	def2-TZVP	def2-TZVPD
NO_3^-	1	−44.3	−43.2	−44.0	−43.3
NO_3^-	2	−54.9	−53.6	−54.4	−53.6
NaCl	1	−13.7	−15.3	−14.8	−14.9
NaCl	2	−15.0	−16.6	−16.3	−16.2
$CHOO^-$	1	−55.7	−57.0	−57.2	−56.9
$CHOO^-$	2	−68.7	−69.8	−70.2	−69.6
NH_4^+	1	−48.0	−48.3	−48.4	−48.4
NH_4^+	2	−54.7	−55.1	−55.3	−55.3
H_3O^+	1	−55.2	−55.4	−55.6	−55.4
H_3O^+	2	−64.9	−65.3	−65.6	−65.4
Glycine	1	−5.8	−6.5	−6.4	−6.4
Glycine	2	−6.2	−7.0	−7.0	−7.0
Benzene	1	−1.5	−1.6	−1.7	−1.7
Benzene	2	−1.9	−2.2	−2.3	−2.2
Phenol	1	−2.7	−3.0	−3.0	−2.9
Phenol	2	−3.5	−3.8	−3.9	−3.7

[a] As defined in Fig. 3.

Table S17: HetPCM solvation energies computed using ωB97M-V theory in various basis sets, using $\varepsilon_{\text{solv}} = 78.4$ and $\varepsilon_{\text{nonp}} = 4$.

Solute	Scheme[a]	ΔG_{elst} (kcal/mol)			
		def2-SVP	def2-SVPD	def2-TZVP	def2-TZVPD
NO_3^-	1	−54.6	−53.0	−54.0	−53.05
NO_3^-	2	−59.8	−58.0	−59.1	−58.1
NaCl	1	−16.9	−18.8	−18.2	−18.3
NaCl	2	−17.6	−19.5	−19.1	−19.1
$CHOO^-$	1	−64.1	−64.5	−65.1	−64.4
$CHOO^-$	2	−70.7	−71.0	−71.7	−70.9
NH_4^+	1	−64.9	−65.2	−65.3	−65.3
NH_4^+	2	−68.2	−68.5	−68.6	−68.6
H_3O^+	1	−72.7	−73.0	−73.1	−72.9
H_3O^+	2	−77.4	−77.8	−78.0	−77.8
Glycine	1	−7.7	−8.6	−8.6	−8.5
Glycine	2	−7.9	−9.0	−8.9	−8.9
Benzene	1	−2.1	−2.4	−2.4	−2.4
Benzene	2	−2.3	−2.6	−2.8	−2.7
Phenol	1	−3.5	−3.9	−3.9	−3.8
Phenol	2	−3.9	−4.3	−4.4	−4.2

[a] As defined in Fig. 3.

Table S18: HetPCM solvation energies computed using ωB97M-V theory in various basis sets, using $\varepsilon_{\text{solv}} = 78.4$ and $\varepsilon_{\text{nonp}} = 10$.

Solute	Scheme^a	ΔG_{elst} (kcal/mol)			
		def2-SVP	def2-SVPD	def2-TZVP	def2-TZVPD
NO_3^-	1	−61.1	−59.2	−60.3	−59.2
NO_3^-	2	−63.0	−61.0	−62.1	−61.1
NaCl	1	−18.9	−21.0	−20.4	−20.6
NaCl	2	−19.2	−21.3	−20.8	−20.9
$CHOO^-$	1	−69.4	−69.3	−70.1	−69.2
$CHOO^-$	2	−71.8	−71.8	−72.6	−71.7
NH_4^+	1	−75.2	−75.4	−75.5	−75.5
NH_4^+	2	−76.4	−76.6	−76.7	−76.7
H_3O^+	1	−83.2	−83.6	−83.7	−83.5
H_3O^+	2	−85.0	−85.4	−85.5	−85.3
Glycine	1	−9.0	−10.2	−10.1	−10.1
Glycine	2	−9.0	−10.4	−10.2	−10.3
Benzene	1	−2.5	−2.8	−2.9	−2.9
Benzene	2	−2.6	−2.9	−3.0	−3.0
Phenol	1	−4.0	−4.5	−4.5	−4.4
Phenol	2	−4.2	−4.7	−4.7	−4.6

[a] As defined in Fig. 3.

Table S19: ωB97M-V/def2-TZVPD solvation energies (in kcal/mol) computed using $\varepsilon_{\text{nonp}} = 1$ or 2.[a]

Solute	Scheme^b	$\varepsilon_{\text{nonp}} = 1, \varepsilon_{\text{solv}} = 78.4$				$\varepsilon_{\text{nonp}} = 2, \varepsilon_{\text{solv}} = 78.4$			
		ΔG_{elst}		Difference		ΔG_{elst}		Difference	
		PEqS^c	HetPCM	Abs.	(%)	PEqS^c	HetPCM	Abs.	(%)
NO_3^-	1	−40.2	−25.5	14.6	(57%)	−49.1	−43.3	5.8	(13%)
NO_3^-	2	−55.2	−46.2	9.0	(20%)	−58.4	−53.6	4.8	(9%)
NaCl	1	−7.3	−8.9	1.6	(17%)	−13.2	−14.9	1.7	(11%)
NaCl	2	−10.4	−10.8	0.3	(3%)	−15.4	−16.2	0.9	(5%)
$CHOO^-$	1	−56.6	−43.6	13.0	(30%)	−64.2	−56.9	7.3	(13%)
$CHOO^-$	2	−70.4	−67.0	3.47	(5%)	−73.8	−69.6	4.2	(6%)
NH_4^+	1	−45.6	−15.1	30.4	(201%)	−58.8	−48.4	10.4	(22%)
NH_4^+	2	−64.5	−29.4	35.2	(120%)	−69.9	−55.3	14.6	(26%)
H_3O^+	1	−54.7	−21.1	33.6	(159%)	−67.3	−55.4	11.9	(21%)
H_3O^+	2	−76.8	−41.1	35.7	(87%)	−80.9	−65.4	15.6	(24%)
Glycine	1	−3.0	−3.1	0.2	(5%)	−4.9	−6.4	1.5	(24%)
Glycine	2	−4.4	−3.8	0.6	(17%)	−6.0	−7.0	1.0	(14%)
Benzene	1	−0.8	−0.5	0.3	(72%)	−1.3	−1.7	0.3	(21%)
Benzene	2	−1.8	−1.5	0.4	(24%)	−2.1	−2.2	0.1	(5%)
Phenol	1	−3.7	−1.5	2.2	(148%)	−4.3	−2.9	1.4	(47%)
Phenol	2	−5.2	−2.9	2.3	(80%)	−5.5	−3.7	1.8	(47%)

[a] See Table 4 for the corresponding HF/def2-TZVPD calculations. [b] Permittivity construction; see Fig. 3. [c] Voronoi construction of $\varepsilon(\mathbf{r})$ using $L = 0.5$ Å, $k = 10$, and a 0.05 Å grid spacing.

Table S20: ωB97M-V/def2-TZVPD solvation energies (in kcal/mol) computed using $\varepsilon_{\mathrm{nonp}} = 4$ or 10.[a]

Solute	Scheme[b]	$\varepsilon_{\mathrm{nonp}} = 4, \varepsilon_{\mathrm{solv}} = 78.4$				$\varepsilon_{\mathrm{nonp}} = 10, \varepsilon_{\mathrm{solv}} = 78.4$			
		ΔG_{elst}		Difference		ΔG_{elst}		Difference	
		PEqS[c]	HetPCM	Abs.	(%)	PEqS[c]	HetPCM	Abs.	(%)
NO_3^-	1	−54.8	−53.05	1.74	(3%)	−59.2	−59.2	0.0	(0%)
NO_3^-	2	−60.1	−58.1	2.0	(3%)	−61.6	−61.1	0.5	(1%)
NaCl	1	−16.8	−18.3	1.5	(8%)	−19.6	−20.6	0.9	(5%)
NaCl	2	−17.9	−19.1	1.2	(6%)	−20.0	−20.9	0.9	(4%)
$CHOO^-$	1	−67.9	−64.4	3.6	(6%)	−71.0	−69.2	1.8	(3%)
$CHOO^-$	2	−73.9	−70.9	3.0	(4%)	−74.0	−71.7	2.2	(3%)
NH_4^+	1	−67.2	−65.3	1.9	(3%)	−73.8	−75.5	1.7	(2%)
NH_4^+	2	−73.4	−68.6	4.8	(7%)	−76.6	−76.7	0.2	(0%)
H_3O^+	1	−75.3	−72.9	2.4	(3%)	−81.8	−83.5	1.7	(2%)
H_3O^+	2	−83.4	−77.8	5.6	(7%)	−85.6	−85.3	0.3	(0%)
Glycine	1	−6.5	−8.5	2.0	(23%)	−8.3	−10.1	1.8	(18%)
Glycine	2	−7.3	−8.9	1.6	(18%)	−8.7	−10.3	1.6	(16%)
Benzene	1	−1.8	−2.4	0.6	(25%)	−2.3	−2.9	0.5	(18%)
Benzene	2	−2.4	−2.7	0.3	(11%)	−2.7	−3.0	0.3	(10%)
Phenol	1	−4.9	−3.8	1.1	(29%)	−5.5	−4.4	1.1	(26%)
Phenol	2	−5.8	−4.2	1.5	(36%)	−6.0	−4.6	1.5	(33%)

[a] See Table 5 for the corresponding HF/def2-TZVPD calculations. [b] Permittivity construction; see Fig. 3. [c] Voronoi construction of $\varepsilon(\mathbf{r})$ using $L = 0.5$ Å, $k = 10$, and a 0.05 Å grid spacing.

S4 pK_a Calculations

Table S21: Relative energies of the imidazolium-flipped acid form to the acid form of various proteins, using atomic radii from Ref. 1.[a]

Protein	ΔE (kcal/mol)[b]			
	gas phase	PCM ($\varepsilon_\mathrm{s} = 78.4$)	HetPCM ($\varepsilon_\mathrm{solv} = 78.4$)	
			$\varepsilon_\mathrm{nonp} = 4$	$\varepsilon_\mathrm{nonp} = 10$
1E5Y	−1.0	1.0	1.6	1.3
1ID2	−4.0	−1.2	1.8	−1.5
1KDI	7.2	3.3	1.6	2.6
1PZA	1.0	0.8	0.3	−7.9
2CAK	−0.0	−0.2	−0.9	−0.4

[a] Analogous to Table 6 but using $R_\mathrm{vdW,C} = 2.124$ Å, $R_\mathrm{vdW,N} = 2.016$ Å, $R_\mathrm{vdW,O} = 1.908$ Å, $R_\mathrm{vdW,S} = 2.52$ Å, and $R_\mathrm{vdW,Cu} = 2.76$ Å, with no atomic spheres used for H. [b] B3LYP+D3(BJ)/6-31+G* level.

Table S22: $\Delta\Delta G_\mathrm{elst}$ between the acid and imidazolium-flipped forms of various proteins.[a]

Protein	$\Delta\Delta G_\mathrm{elst}$ (kcal/mol)			
	gas phase	PCM ($\varepsilon = 78.4$)	HetPCM ($\varepsilon_\mathrm{solv} = 78.4$)	
			$\varepsilon_\mathrm{nonp} = 4$	$\varepsilon_\mathrm{nonp} = 10$
1E5Y	5.9	1.7	−0.5	0.8
1ID2	8.9	3.1	1.9	2.6
1PZA	4.0	1.1	−0.1	0.6
2CAK	4.1	1.5	3.7	2.3

[a] B3LYP+D3(BJ)/6-31+G* level.

Table S23: Solvation energies for protein models computed using different PCM boundary conditions in conjunction with united-atom radii from Ref. 1.[a]

Protein	ΔG_elst (kcal/mol)[b]								
				HetPCM ($\varepsilon_\mathrm{solv} = 78.4$)					
	PCM ($\varepsilon_\mathrm{s} = 78.4$)			$\varepsilon_\mathrm{nonp} = 4$			$\varepsilon_\mathrm{nonp} = 10$		
	Base	Acid	Flipped	Base	Acid	Flipped	Base	Acid	Flipped
1E5Y	−66.3	−97.3	−95.2	−49.6	−76.1	−73.5	−59.9	−89.3	−87.1
1ID2	−70.4	−104.7	−101.9	−52.0	−82.3	−80.1	−63.4	−96.3	−93.7
1KDI	−65.2	−97.4	−101.3	−48.8	−76.5	−82.0	−59.0	−89.5	−94.0
1PZA	−72.5	−97.0	−97.3	−54.0	−75.8	−76.6	−65.5	−89.1	−97.3
2CAK	−60.7	−98.9	−99.1	−45.9	−78.1	−79.0	−55.1	−91.1	−91.5

[a] Analogous to Table 7 but using $R_\mathrm{vdW,C} = 2.124$ Å, $R_\mathrm{vdW,N} = 2.016$ Å, $R_\mathrm{vdW,O} = 1.908$ Å, $R_\mathrm{vdW,S} = 2.52$ Å, and $R_\mathrm{vdW,Cu} = 2.76$ Å, with no atomic spheres used for H. [b] B3LYP+D3(BJ)/6-31+G* level.

Table S24: pK_a for the acid and imidazolium-flipped forms of Cu proteins, along with the average of the two.[a]

Protein	Gas Phase		PCM ($\varepsilon_\mathrm{s} = 78.4$)		HetPCM ($\varepsilon_\mathrm{nonp} = 4$)[b]		HetPCM ($\varepsilon_\mathrm{nonp} = 10$)[b]	
	pK_a	error[c]	pK_a	error[c]	pK_a	error[c]	pK_a	error[c]
Acid								
1E5Y	4.70	2.70	2.71	0.71	3.23	1.23	2.95	0.95
1ID2	4.63	2.57	5.77	1.43	6.45	0.75	6.06	1.14
1KDI	4.40	0.00	4.40	0.00	4.40	0.00	4.40	0.00
1PZA	13.33	8.93	6.33	1.93	8.04	3.64	7.03	2.63
2CAK	−2.40	4.40	2.95	0.95	−0.66	2.66	1.59	0.41
Flipped Acid								
1E5Y	9.04	7.04	3.94	1.94	2.85	0.85	3.57	1.57
1ID2	11.15	3.95	8.05	0.85	7.84	0.64	7.99	0.79
1KDI	4.40	0.00	4.40	0.00	4.40	0.00	4.40	0.00
1PZA	16.24	11.44	7.11	2.31	7.94	3.14	7.47	2.67
2CAK	0.62	1.38	4.08	2.08	2.02	0.02	3.29	1.29
Average								
1E5Y	6.87	4.87	3.33	1.33	3.04	1.04	3.26	1.26
1ID2	7.89	0.69	6.91	0.29	7.14	0.06	7.03	0.17
1KDI	4.40	0.00	4.40	0.00	4.40	0.00	4.40	0.00
1PZA	14.79	9.99	6.72	1.92	7.99	3.19	7.25	2.45
2CAK	−0.89	2.89	3.52	1.52	0.68	1.32	2.44	0.44

[a] B3LYP+D3(BJ)/6-31+G* level. These data are plotted in Fig. 6. [b] $\varepsilon_\mathrm{solv} = 78.4$ used for HetPCM. [c] Errors relative to experimental values: p$K_\mathrm{a} < 2$ for 1E5Y and 2CAK,[4–8] p$K_\mathrm{a} = 7.2$ for 1ID2,[9] p$K_\mathrm{a} = 4.4$ for 1KDI,[10] and p$K_\mathrm{a} = 4.8$ for 1PZA.[11] 1KDI is used as a reference value; see eq. 34.

References

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