Supplementary Material

The Voronoi volumes published by Schaefer *et al.* (J. Comput. Chem., 2001), used with ACE to compute electrostatic solvation free energies, give reasonable correlation with FEP results over the full set of amino acids, but with noticeable systematic errors. The magnitude of the solvation free energies of the positively charged residues (Lys and Arg) are grossly over-estimated, while those of the remainder of the amino acids are systematically under-estimated (Figure 1, red points). The over-estimation of the solvation energies of Lys and Arg were identified as being a result of the combination of a high charge density and zero volume for the charged-group protons (atom type HC); the under-estimation of the remaining energies suggests that the Voronoi volumes are uniformly larger that optimal. An optimized set of volumes was generated by a simple procedure. First, all volumes were uniformly scaled (over intervals of 0.01) until the RMS error between the ACE and FEP solvation free energies of all amino acids, *with the exception of Lys and Arg*, was at a minimum; the optimal scaling factor was 0.67. The volume of HC was then systematically increased from zero to minimize the RMS error over the full set of amino acid (including Lys and Arg); the optimal HC volume was 9.39 $Å^3$. These optimized volumes give significantly improved agreement with FEP results. (Figure 1, blue points). The details of how each perturbation affects the error are listed in Table 1. ***Note:*** *All FEP solvation energies were taken from Nina* et al. *(J. Phys. Chem. B, 1997).*

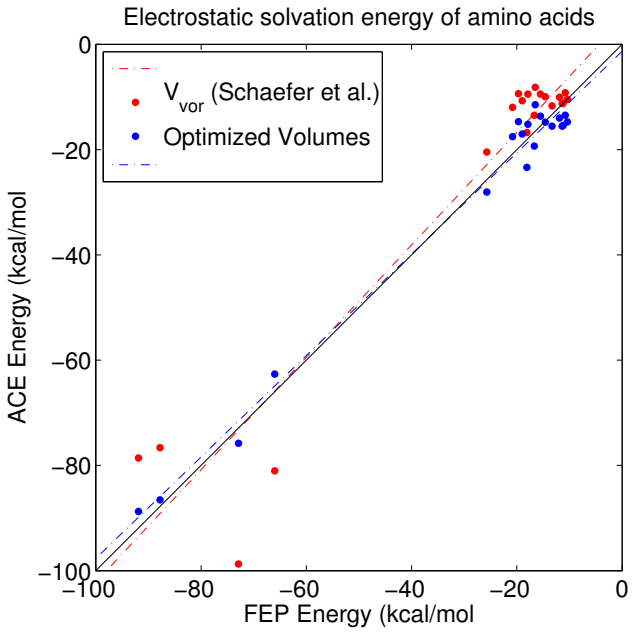

Figure 1: **ACE solvation energies with standard and optimized volumes.**

Table 1: Optimization of ACE volumes for amino acids.

Volume Set:	V_{vor}[a]	$0.67 \cdot V_{vor}$[a]	$0.67 \cdot V_{vor}$[a] + V(HC) = 9.79 Å^3
All amino acids			
RMS Error[b]	9.21	10.4	3.29
Max. Error[b]	25.8	35.1	5.27
R^2	0.91	0.92	0.98
All amino acids, except Lys and Arg			
RMS Error[b]	6.68	3.31	3.31
Max. Error[b]	13.3	5.27	5.27
R^2	0.98	0.98	0.98
Non-charged amino acids			
RMS Error[b]	5.60	3.41	3.41
Max. Error[b]	10.3	5.27	5.27
R^2	0.32	0.44	0.44

[a] Voronoi volumes for the all-atom PARAM22 parameter set for proteins (Schaefer et al, 2001).
[b] Errors in kcal/mol.