

## Reply to “Comments on ‘Refinement of COSMO–SAC and the Applications’”

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Sir: We agree that the mathematical formula for  $\Delta G^{\text{res}}$  in COSMO–SAC is equivalent to the expression for  $\mu$  in COSMO–RS, and we have acknowledged this previously.<sup>1</sup> However, as we have also explained in our previous work,<sup>1</sup> there are significant differences the derivations and interpretations of these equations.

There are also important differences in implementation between COSMO–RS and COSMO–SAC (for example, the differences in taking hydrogen bonding into account<sup>2,3</sup> that are discussed below). Moreover, COSMO–SAC and COSMO–RS have been evolving on different paths; we present all of our changes to COSMO–SAC openly in journals, so that everyone can understand fully the details of the methodology, whereas some of the details of COSMO–RS remain buried in proprietary code.

In response to our statement about the consistency of the values  $r_{\text{av}}$  and  $r_{\text{eff}}$ , Klamt and Eckert in their comment state that “it has been discussed by us that the discrepancy of  $r_{\text{av}}$  and  $r_{\text{eff}}$  is highly significant, but not understood.” Our interpretation is presented in the paper in question,<sup>3</sup> where we justify the need for a decay parameter  $f_{\text{decay}}$ . We agree with Klamt and Eckert that we should include this in the number of parameters in COSMO–SAC. However, we do not treat this decay factor as an adjustable parameter, because its value was determined previously. Furthermore, by comparison of the two models, it is clear that no single value of  $r_{\text{eff}}$  corresponds to  $f_{\text{decay}}$ . To mimic the effect of the single-constant  $f_{\text{decay}}$  in COSMO–SAC would require different values of  $r_{\text{eff}}$  for each species in COSMO–RS. Therefore, the two approaches are mathematically different; they are not alike as claimed by Klamt and Eckert.

The meaning of  $q$  is the segment charge after  $\sigma$ -averaging, as explained in the work by Lin et al.<sup>2</sup> The dielectric energy ( $E_{\text{diel}}$ ) is the energy needed to account for the dielectric polarization, which is equal to half of the interaction energy of the solute with the screening charges ( $E_{\text{diel}} = 1/2\Phi q$ ). This formulation is true both before and after the averaging.

We state that our hydrogen-bonding term is chemically based, because we apply the hydrogen-bonding correction only to those molecular interactions that are known from chemistry to lead to strong hydrogen bonding (e.g., H, O, N, S). We do not include such interactions for atoms that do not lead to significant hydrogen bonding (e.g., C, Si, etc.) or for those that lead only to weak hydrogen bonding (such as that which occurs with Cl in HCl). In our model, the likelihood of hydrogen-bond formation between atom types that are known to form hydrogen

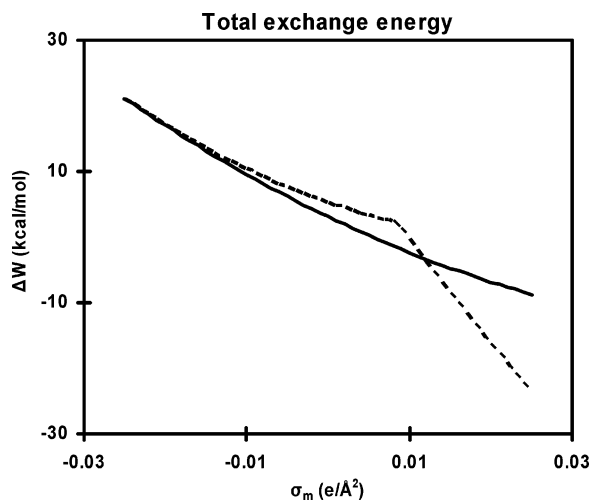
bonds is dependent on the computed charge densities. For this reason, we separate the sigma profile of a molecule into one part for the hydrogen-bonding atoms and a second part for those that do not form hydrogen bonds, as explained in refs 2 and 3. This is fundamentally different from the method used in COSMO–RS, which allows hydrogen bonding between all atoms (even C and Si), depending only their charge densities.

We agree with Klamt and Eckert that it seems physically reasonable to allow a temperature dependence of the hydrogen-bonding effect. Indeed, we considered this possibility in our parameter optimization. However, we did not obtain a significant improvement in the model by including this effect. We believe that this result is because the decay in hydrogen bonding with increasing temperature is greatly dependent on the species involved. For example, hydrogen-bond energies vary from 8 kJ/mol for N–H···O, to 21 kJ/mol for O–H···O and 155 kJ/mol for F–H···F. Therefore, we consider that it is not plausible that a single temperature decay function with fixed parameters should apply to all hydrogen bonds, which is the procedure Klamt uses.

In terms of the number of adjustable parameters in our model, we agree with Klamt and Eckert that we should include  $\sigma_0$  in eq 16 of our original paper.<sup>3</sup> This leads to another difference between our hydrogen-bonding model and that in COSMO–RS. Using a fixed cutoff ( $\sigma_{\text{hb}}$ ) for hydrogen-bonding interactions, COSMO–RS has a discontinuity in the derivative of the potential surface, denoted as  $\Delta W(\sigma_m, \sigma_n)$ , relative to charge density (we referred to this as a step change in the hydrogen bonding). In contrast, COSMO–SAC has no derivative discontinuity; this is shown in Figure 1 for water with segments of varying charge density.

The 10 element-specific radii used in COSMO–SAC were the predetermined set (based on the work of Klamt) used in the DMol<sup>3</sup> quantum chemistry package. Although the program allows the user to redefine the radii, we did not do so. These parameters were assumed to be fixed and not part of our parameter optimization process. Consequently, in the discussion of the number of parameters in COSMO–SAC, we counted only those parameters whose values we optimized, not those contained within the quantum mechanics packages.

Reference 4 discusses how different conformers are treated in COSMO–RS. The procedure starts with a collection of local minimum energy structures conformers from single-molecule density functional theory (DFT) calculations. The population of each conformer in the solvent is then calculated using the



**Figure 1.** Derivative of the potential surface ( $\Delta W$ ), relative to charge density ( $\sigma_m$ ). The dotted line represents COSMO-RS in eq 11 from the referenced work,<sup>3</sup> using values of  $c_{hb} = 85579 \text{ kcal/mol } \text{\AA}^4/\text{e}^2$ ,  $\sigma_{hb} = 0.0084 \text{ e}/\text{\AA}^2$ ,  $f_{hb}(T) = 1$ , and  $\sigma_n = -0.025 \text{ e}/\text{\AA}^2$ ; the solid line represents COSMO-SAC in eq 12 from the referenced work,<sup>3</sup> using values of  $c_{hb} = 3484.42 \text{ kcal/mol } \text{\AA}^4/\text{e}^2$  and  $\sigma_n = -0.025 \text{ e}/\text{\AA}^2$ .

Boltzmann weighting factor, based on the transfer of free energy to the solvent. However, we have shown, from molecular dynamics (MD) calculations,<sup>5</sup> that many molecular configura-

tions of the solute stable in the solvent are not stable in the single-molecule calculations. Therefore, using a weighted average of the conformations found from single-molecule calculations, as done in COSMO-RS, although a good first step, does not address the molecular conformation issue adequately.

Finally, Klamt and Eckert comment on COSMO files generated using the Jaguar quantum chemistry program from Schrödinger, Inc. This comment is not relevant to the paper<sup>3</sup> that Klamt and Eckert are addressing their comments, because our referenced paper<sup>3</sup> used only results from Dmol<sup>3</sup>. Our earlier paper<sup>2</sup> did use Jaguar COSMO results. Schrödinger has not yet released a version of Jaguar including the COSMO method. The COSMO results so produced (jcosmo files), and used in Lin et al.,<sup>2</sup> can be obtained from S.-T. Lin at stlin@ntu.edu.tw.

#### Literature Cited

- (1) Lin, S. T.; Sandler, S. I. *Ind. Eng. Chem. Res.* **2002**, *41*, 2332.
- (2) Lin, S. T.; Chang, J.; Wang, S.; Goddard, W. A.; Sandler, S. I. *J. Phys. Chem. A* **2004**, *108*, 7429.
- (3) Wang, S.; Sandler, S. I.; Chen, C.-C. *Ind. Eng. Chem. Res.* **2007**, *46*, 7275–7288.
- (4) Klamt, A. *COSMO-RS: From Quantum Chemistry to Fluid Phase Thermodynamics and Drug Design*; Elsevier: New York, 2005.
- (5) Wang, S.; Stubbs, J. M.; Siepmann, J. I.; Sandler, S. I. *J. Phys. Chem. A* **2005**, *109* (49), 11285.

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