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A Comprehensive Comparison of the IEFPCM and SS(V)PE Continuum Solvation Methods with the COSMO Approach

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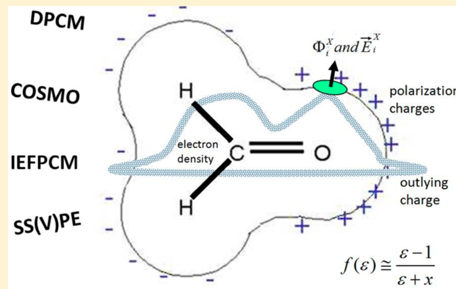
Supporting Information

ABSTRACT: Dielectric continuum models are popular for modeling solvent effects in quantum chemical calculations. The polarizable continuum model (PCM) was originally published exploiting the exact dielectric boundary condition. This is nowadays called DPCM. The conductor-like screening model (COSMO) introduced a simplified and slightly empirical scaled conductor boundary condition, which turned out to reduce the errors resulting from outlying charge. This was implemented in PCM as CPCM. Later, the integral equation formalism (IEFPCM) and the formally identical SS(V)PE model of Chipman introduced a modified dielectric boundary condition combining the dielectric exactness of DPCM with the reduced outlying charge sensitivity of COSMO. In this paper, we demonstrate on two huge data sets of neutral and ionic solutes that no significant difference can be observed between the COSMO and IEFPCM, if the correct scaling factor is chosen for COSMO.



■ INTRODUCTION

The dielectric continuum approach is the most widely used class of methods for modeling solvent effects in quantum chemical calculations, and the apparent surface charge (ASC) models comprise the most popular subclass of these.[1] Its first representative is the polarizable continuum model (PCM),[2] which was originally published using the exact dielectric boundary condition (EDBC) for the calculation of the vector of polarization charge densities σ on the surface segments of the solute cavity Γ. Later, this original version got named DPCM. In 1993, Klamt and Schüürmann presented the completely independently derived conductor-like screening model (COSMO),[3] which makes use of the much simpler boundary condition of a conductor and takes into account the reduction of the polarization charge densities occurring at finite permittivity ε by a slightly empirical scaling x

$$f(\varepsilon) = \frac{\varepsilon - 1}{\varepsilon + x} \tag{1}$$

where x was argued to be optimally chosen as 0.5 for neutral solutes, whereas, for ions, $x = 0$ should be the best choice. Theoretically, COSMO is exact in the limit of $\varepsilon \to \infty$, but the finite ε behavior is slightly approximate. A big advantage of COSMO over the EDBC was the fact that it only requires the solute electrostatic potential $\underline{\Phi}^X$ on the cavity of solute X, while the EDBC requires the normal component of the solute electric field $\underline{E}_n^X$, which is much more complicated to calculate and more sensitive to numerical noise. However, the main advantage was only detected later: COSMO suffers much less from outlying charge errors (OCE)[4] than solvation models using the EDBC, because $\underline{\Phi}^X$ is an order of magnitude less influenced than $\underline{E}_n^X$ by the fact, that in continuum solvation models, almost inevitably some small part of the total electron density of the solute is located outside the solute cavity, whereas the dielectric continuum approach assumes to find all solute charge inside the cavity. These advantages of the COSMO method motivated Barone and Cossi to implement the COSMO boundary condition within the PCM framework, resulting in the so-called CPCM model.[5] Unfortunately, the default value for x in the COSMO scaling function was set to zero in CPCM, and not to 0.5, as in the original COSMO. Cossi et al. later showed that the agreement of the results of DPCM and CPCM improves, if, for neutral compounds, a value of $x = 0.5$ is chosen; i.e., they confirmed that the original COSMO choice of x is preferable.[6] However, the official releases of CPCM in the Gaussian program[7] do not allow the user to set this value. Hence, CPCM is most often used with an unfavorable scaling function.

In 1997, Chipman[8] started to develop a number of alternative boundary conditions for ASC continuum solvation models with the special focus of taking into account the volume polarization caused by the charge density outside the cavity. As the computationally most practical result, he derived the SS(V)PE model, in which the (V) denotes approximate volume polarization. As COSMO, this model does only require the electrostatic potential vector $\underline{\Phi}^X$ on the cavity and avoids using the electrostatic field normal components $\underline{E}_n^X$. At the costs of

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being numerically more expensive than COSMO, it does not require any empirically adjusted parameter beyond the cavity definition itself, which is empirical in all CSMs.

In 1997, Cances et al.[9] published a new and rather general framework for ASC continuum solvation models, the so-called integral equation formalism IEF, which even allowed for the description of anisotropic dielectric continua. A year later, a simplified and computationally much more efficient version of the IEF was presented by Mennucci et al.,[10] which was now again restricted to isotropic solvents, but avoided the use of the problematic $\underline{E}_n^X$. Later, it turned out that this method, which is nowadays used under the name IEFPCM, is identical with Chipman's SS(V)PE, as proven in the excellent theoretical comparison of the different ASC solvation models by Chipman. A third, COSMO-based derivation of the same equation, was proposed by Klamt while studying the original IEFPCM publication in 1997. This derivation, which was published in Chipman's paper, elucidates the close similarity between COSMO and SS(V)PE/IEFPCM.[11]

Summarizing the situation, the SS(V)PE/IEFPCM equation has been independently derived by three groups and is currently considered as the best available boundary condition for ASC isotropic dielectric continuum solvation models, combining a robustness with respect to outlying charge effects and computational efficiency. From the theoretical equations, it is obvious that, in the limit of $\varepsilon \to \infty$, SS(V)PE/IEFPCM must be identical to the older COSMO model, which is the algorithmically simplest and computationally least demanding of all ASC models. For finite values of ε, COSMO is slightly more empirical. However, it is not known how big the deviations of COSMO and SS(V)PE/IEFPCM are in practice and whether the additional complexity of SS(V)PE/IEFPCM is really warranted by more accurate results. Therefore, in this paper, we investigate systematically the practical differences of COSMO and SS(V)PE/IEFPCM solvation models.

■ THEORY

Using the notations introduced in the COSMO paper, the three methods considered here can be described as follows. Let us start with a solute X and a closed cavity Γ defining the boundary of the dielectric continuum of strength ε embedding X. Let Γ be represented by m sufficiently small surface segments. Let $\underline{\sigma}$ be the vector of the m polarization charge densities on the segments, and $\underline{\underline{S}}$ shall be a diagonal matrix of the m segment areas. Let $\underline{\underline{A}}$ be the symmetric Coulomb interaction matrix of the charges on the segments, with diagonal elements representing the self-interactions. Let $\underline{\Phi}^X$ be the vector of the solute electrostatic potential on the m segments, and $\underline{E}_n^X$ the corresponding vector of the electrostatic field normal components. Then, the exact dielectric boundary condition used in DPCM reads

$$4\pi\underline{\sigma} = \frac{\varepsilon - 1}{\varepsilon + 1}[\underline{E}_n^X + \underline{\underline{D}}\,\underline{\underline{S}}\,\underline{\sigma}] \tag{2}$$

where $\underline{\underline{D}}$ is the nonsymmetric matrix generating the electric field normal vectors resulting from the polarization charges on the m segments. The COSMO boundary condition reads

$$0 = \frac{\varepsilon - 1}{\varepsilon + x}\underline{\Phi}^X + \underline{\underline{A}}\,\underline{\underline{S}}\,\underline{\sigma} \tag{3}$$

For $\varepsilon = \infty$, this simply is the grounded conductor boundary condition of vanishing total potential on the conductor surface.

As mentioned above, the SS(V)PE/IEFPCM boundary condition can be easily derived from a combination of the EDBC and the COSMO boundary condition. If we introduce $\underline{\sigma}^*$ as the polarization charge densities produced in the limit of infinite ε and if we make use of the fact that, under the assumption of all solute charge being inside the cavity, the polarization charges arising from the conductor boundary condition must be identical with those resulting from the EDBC, then we get

$$\underline{E}_n^X = [4\pi\underline{\underline{I}} - \underline{\underline{D}}\,\underline{\underline{S}}]\underline{\sigma}^* \tag{4}$$

and

$$\underline{\sigma}^* = -\underline{\underline{A}}^{-1}\underline{\underline{S}}^{-1}\underline{\Phi}^X \tag{5}$$

Inserting eq 5 into eq 4, we get

$$\underline{E}_n^X = -[4\pi\underline{\underline{I}} - \underline{\underline{D}}\,\underline{\underline{S}}]\underline{\underline{A}}^{-1}\underline{\underline{S}}^{-1}\underline{\Phi}^X = [\underline{\underline{D}} - 4\pi\underline{\underline{S}}^{-1}]\underline{\underline{A}}^{-1}\underline{\Phi}^X \tag{6}$$

Now, we can use this expression for replacing the problematic electric field normal vector $\underline{E}_n^X$ in the EDBC, i.e., in eq 2, yielding

$$4\pi\underline{\sigma} = \frac{\varepsilon - 1}{\varepsilon + 1}[\underline{\underline{D}} - 4\pi\underline{\underline{S}}^{-1}]\underline{\underline{A}}^{-1}\underline{\Phi}^X + \frac{\varepsilon - 1}{\varepsilon + 1}\underline{\underline{D}}\,\underline{\underline{S}}\,\underline{\sigma} \tag{7}$$

which, after short reorganization, yields the SS(V)PE/IEFPCM boundary condition

$$\left[4\pi\underline{\underline{I}} - \frac{\varepsilon - 1}{\varepsilon + 1}\underline{\underline{D}}\,\underline{\underline{S}}\right]\underline{\sigma} = \frac{\varepsilon - 1}{\varepsilon + 1}[\underline{\underline{D}} - 4\pi\underline{\underline{S}}^{-1}]\underline{\underline{A}}^{-1}\underline{\Phi}^X \tag{8}$$

This derivation clearly shows that the more favorable behavior of SS(V)PE/IEFPCM compared to the EDBC and thus DPCM, which sometimes is argued to result from taking into account volume polarization, just arises from replacing the problematic electric field normal vector $\underline{E}^X_{;\ n}$ based on a COSMO expression. It also shows that SS(V)PE/IEFPCM is algorithmically much more complicated and expensive and more sensitive to numerical noise than COSMO, because it requires the nonsymmetric $\underline{\underline{D}}$-matrix of the electric field normal components generated by the screening charges in addition to the symmetric COSMO matrix $\underline{\underline{A}}$.

■ METHODS

For a comparison of the different ASC boundary conditions, it is required that one uses an otherwise identical implementation of the dielectric continuum solvation methods in a quantum chemical package, because any differences in the cavity construction can easily cause much larger deviations than those arising from different choices of the boundary conditions. For that reason, we have chosen the Gaussian 09 software,[7] which offers DPCM, CPCM, and IEFPCM as options. Since SS(V)PE and IEFPCM are identical and since IEFPCM is the name of the method in Gaussian 09, we will denote the SS(V)PE/IEFPCM method shortly as IEFPCM further on. Unfortunately, there is no explicit keyword to change the x parameter in the COSMO scaling function, which is set to zero in Gaussian 09. Nevertheless, this lack can be easily overcome by using an effective value $\tilde{\varepsilon}(\varepsilon, x)$ of the dielectric permittivity ε, which results in the same value of the scaling function as if a special value of x would have been used. It is defined by

$$\frac{\tilde{\varepsilon}(\varepsilon, x) - 1}{\tilde{\varepsilon}(\varepsilon, x)} = \frac{\varepsilon - 1}{\varepsilon + x} \tag{9}$$

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Table 1. Statistical Measures for the Comparison of Dielectric Solvation Energy of Neutral Compounds Obtained by CPCM and DPCM to Those by IEFPCM

		RMSD (kcal/mol)					r^2				
	α	0.9	1	1.1	1.2	1.3	0.9	1	1.1	1.2	1.3
IEFPCM $\varepsilon = 2$	CPCM $x = 0.50$	0.151	0.107	0.078	0.059	0.045	0.992	0.993	0.993	0.993	0.993
	CPCM $x = 0.45$	0.130	0.094	0.071	0.056	0.044	0.992	0.993	0.993	0.993	0.993
	CPCM $x = 0$	0.660	0.484	0.373	0.294	0.235	0.993	0.993	0.993	0.993	0.994
	DPCM	0.505	0.212	0.118	0.061	0.030	0.914	0.960	0.982	0.992	0.997
IEFPCM $\varepsilon = \infty$	CPCM	0.000	0.000	0.000	0.000	0.000	1.000	1.000	1.000	1.000	1.000
	DPCM	1.268	0.758	0.419	0.210	0.103	0.894	0.945	0.976	0.990	0.996

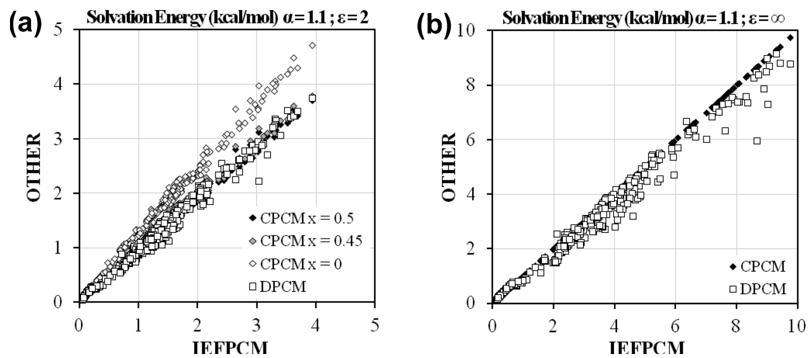

Figure 1. (a) Dielectric solvation energies for DPCM, CPCM (x = 0, 0.5, 0.45) for 318 neutral compounds at a dielectric permittivity of 2. (b) Same differences for dielectric permittivity ∞. Only one CPCM line is plotted, because the different x values yield identical results in this limit. All data points are plotted vs the IEFPCM result.

and thus yields

$$\tilde{\varepsilon}(\varepsilon, x) = \frac{\varepsilon + x}{x + 1} \tag{10}$$

In this way, we considered three variants of CPCM, one corresponding to the Gaussian 09 default (CPCM with $x = 0$), one corresponding to the $x = 0.5$, as suggested in the original COSMO implementation, and one with an optimized value of x in order to achieve optimal agreement with IEFPCM.

In addition to the variation of the methods and x parameter, we modified the radii scaling parameter in 0.1 steps from 0.9 to 1.3. The default value is 1.1. By choosing the smaller radii, we could study the behavior of the different methods in the limit of large amounts of outlying charge, and with the large radii, the amount of outlying charge is reduced to very small amounts.

All quantum calculations have been performed using the density functional theory using the BVP86/TZVP/DGA1 computational level.[12−14]

All dielectric solvation energies are reported as differences between total energies in vacuum and in the dielectric continuum, employing the different dielectric continuum models.

■ DATA SETS

In order to perform a rigorous comparison, we looked for a representative and unbiased set of compounds to be considered in the study. We decided to consider the 318 neutral solutes in the SM8 solvation free energy data set,[15] which has been considered in other comparisons of solvation models before.[16] This choice should guarantee that all major compound classes, for which experimental solvation data are available, are represented. The geometries were taken from the BP-TZVP gas phase geometry optimizations recently published in a study on the D-COSMO-RS solvation model.[17]

For the ions, we selected a set of 20 diverse anions and 20 diverse cations from the COSMObaseIL database for ionic liquids.[18]

The coordinates for all 358 compounds are given in the Supporting Information.

The differences between the dielectric solvation energy obtained by the continuum models were quantified by calculating the root-mean-square deviation (RMSD) using IEFPCM as reference:

$$\mathrm{RMSD} = \sqrt{\frac{\sum (E - E_{\mathrm{IEFPCM}})^2}{n}} \tag{11}$$

■ RESULTS

Neutral Solutes. For all 318 neutral solutes, first the vacuum energy was calculated. Then, dielectric continuum solvation models were performed for 50 different parameter combinations:

(1) Dielectric permittivity ε: 2 and ∞ (represented as 9999).
(2) Radii scaling factor α: 0.9, 1.0, **1.1**, 1.2, 1.3.
(3) CSM variant: IEFPCM, DPCM, CPCM (x = 0.0, 0.5, 0.45, 0.37, 0.43).

Thus, in total, 51∗318 = 16218 quantum calculations have been performed for the neutral compounds. All results are reported in Table SI1, except for CPCM with x = 0.37 and 0.43, which are considered as intermediate results for finding

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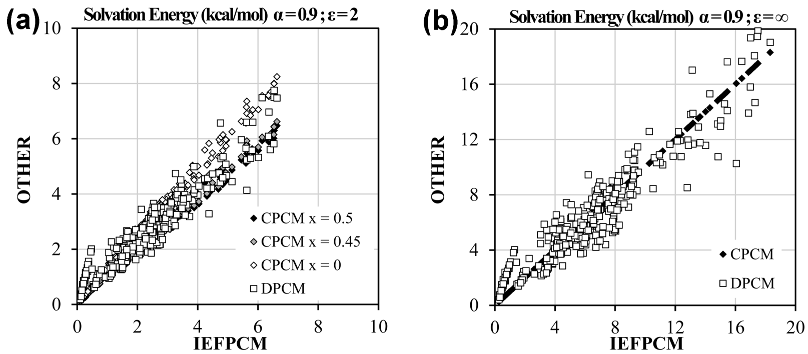

Figure 2. Same data as shown in Figure 1, but here for smaller cavity radii, i.e., α = 0.9.

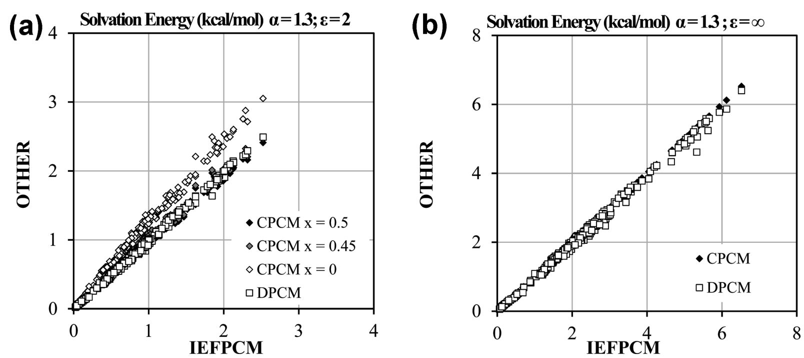

Figure 3. Same data as shown in Figure 1, but here for larger cavity radii, i.e., α = 1.3.

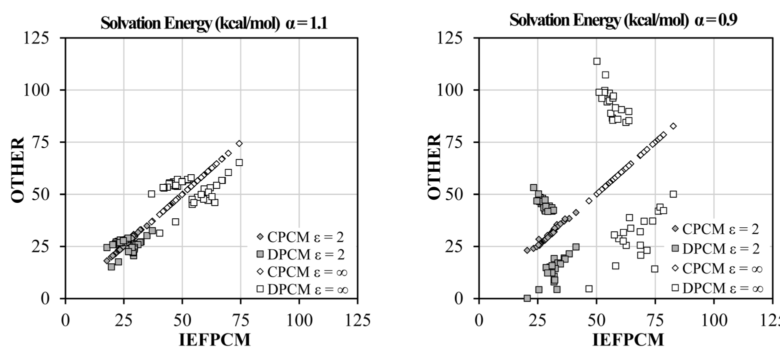

Figure 4. Dielectric solvation energies for 40 ions for (a) default radii with α = 1.1 and (b) reduced cavity radii with α = 0.9.

the optimal x value of 0.45. Table 1 shows the statistical measures for all calculations for neutrals.

Figure 1 shows the results for the default cavity size (α = 1.1) and dielectric permittivity of ε = 2 and ∞, respectively. Table 1 shows the statistical measures for all calculations for neutrals, except for CPCM with x = 0.37 and 0.43, which are considered as intermediate results for finding the optimal x value of 0.45. As theoretically expected, in the limit of $\varepsilon = \infty$, a perfect agreement of CPCM and IEFPCM is achieved. DPCM shows substantial deviations resulting from the outlying charge problem. The largest deviation of DPCM arises for methyl 3-methyl-4-thiomethoxyphenylthiophosphate, for which DPCM underestimates the screening energy by more than 25%. At the lower limit of solvent dielectric constants, i.e., for ε = 2, CPCM with x = 0, i.e., the default CPCM in Gaussian, overestimates the dielectric solvation energies systematically, resulting in an RMSD of 0.37 kcal/mol, but with an excellent correlation of r^2 = 0.993, while CPCM with the original COSMO default x = 0.5 yields the same excellent correlation, but a RMSD of only 0.073 kcal/mol. The best agreement between IEFPCM and CPCM can be achieved using x = 0.45, reducing the RMSD to 0.071 kcal/mol. Nevertheless, we do not consider this small decrease to be relevant. We thus propose to stay with x = 0.5 for neutral solutes.

Figures 2 and 3 show the same plots as Figure 1, but now at reduced cavity radii (α = 0.9) and increased cavity radii (α = 1.3). At reduced cavity radii, all solvation energies are increased, and the amount of outlying charge is much larger than that for α = 1.1. For the larger cavities, i.e., α = 1.3, the deviations decrease and the correlation between DPCM and IEFPCM strongly increases at both ε = 2 and $\varepsilon = \infty$. However, the effect of the outlying charge on the CPCM and IEFPCM is nearly identical. At $\varepsilon = \infty$, there still is no difference, and at ε = 2, the correlation coefficients between all CPCM variants and IEFPCM stay the same as they were at α = 1.1. They also stay unchanged for α = 1.3. As clearly visible in Figure 3, DPCM converges against IEFPCM in the limit of almost vanishing outlying charge.

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Table 2. Statistical Measures for the Comparison of Dielectric Solvation Energy of Ionic Solutes Obtained by CPCM and DPCM to Those by IEFPCM

		RMSD (kcal/mol)					r^2				
	α	0.9	1	1.1	1.2	1.3	0.9	1	1.1	1.2	1.3
IEFPCM	CPCM	0.96	0.58	0.48	0.43	0.40	0.966	0.991	0.994	0.994	0.994
$\varepsilon = 2$	DPCM	18.73	9.40	4.76	2.40	1.22	0.158	0.102	0.046	0.673	0.926
IEFPCM	CPCM	0.00	0.00	0.00	0.00	0.00	1.000	1.000	1.000	1.000	1.000
$\varepsilon = \infty$	DPCM	38.55	19.10	9.60	4.81	2.46	0.289	0.147	0.047	0.709	0.937

Ionic Solutes. For the 40 ions, again $\varepsilon = 2$ and $\varepsilon = \infty$ are considered, but for CPCM, only $x = 0$ is considered, since this is the default of CPCM and it agrees with the x value for ions suggested in the original COSMO publication. As for the neutral solutes, five values of the radii scaling factor α are considered.

Figure 4 shows the dielectric solvation energies of all ions calculated with CPCM ($x = 0$) and DPCM at $\varepsilon = 2$ and $\varepsilon = \infty$, plotted versus the respective IEFPCM results. The statistics of all ion results are given in Table 2. Again, a perfect agreement of CPCM and IEFPCM is achieved at $\varepsilon = \infty$, and with a correlation coefficient of $r^2 = 0.993$, an almost perfect agreement of the two methods is also achieved at $\varepsilon = 2$. DPCM again suffers dramatically from the outlying charge effect. The correlation coefficient of the DPCM results vs the IEFPCM results is as low as $r^2 = 0.047$ at both values of ε. All dielectric solvation energies for anions are underestimated by DPCM, because the complete neglect of the outlying electron density reduces the effective charge of anions. The opposite happens for cations. For the reduced cavity radii, the outlying charge errors of DPCM become so large that even an inverse correlation with IEFPCM occurs.

Zwitterionic Solutes. After finishing our project, the interesting question was raised about which choice of the x parameter should be used for neutral and charged zwitterions, respectively. Therefore, we added a small study on four neutral zwitterionic amino acids and two charged zwitterions. For all of them, we performed calculations with IEFPCM and CPCM with $x = 0.5$ and $x = 0$. The results are shown in Figure 5, and detailed data are given in Table SI1. When using the default value of x, according to the overall charge of the solute, i.e., $x = 0.5$ for the neutral zwitterions and $x = 0$ for the ionic zwitterions, a correlation coefficient of $r^2 = 0.9977$ is achieved between the CPCM and IEFPCM results. Forcing the regression line to zero offset still leaves an excellent correlation of $r^2 = 0.988$. Therefore, it appears that the choice of x should be made according to the overall charge of the solute even for zwitterions.

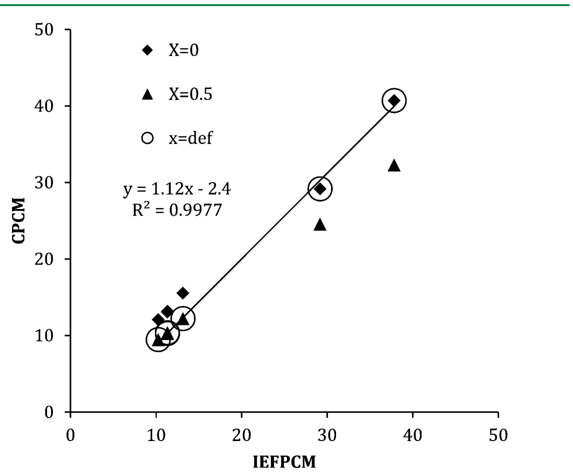

Figure 5. Dielectric solvation energies (kcal/mol) for 4 neutral and 2 charged zwitterions. The data for glutamine and glycine are indistinguishably close.

CONCLUSIONS

The integral equation formalism in its second version, as implemented in Gaussian 09, and the formally identical SS(V)PE formalism are widely accepted as the currently best compromise between theoretical exactness and computational efficiency for dielectric solvation models. Nevertheless, almost identical dielectric solvation energies can be achieved by the simpler COSMO method when using the originally proposed dielectric scaling factor with the empirical parameter $x = 0.5$ for neutral solutes and $x = 0$ for ions. With this choice of x, COSMO is essentially as good as IEFPCM/SS(V)PE not only in highly dielectric solvents but also in nonpolar solvents. Furthermore, the general identity of IEFPCM/SS(V)PE and COSMO in the limit of $\varepsilon = \infty$ and the excellent agreement of COSMO and IEFPCM/SS(V)PE at $\varepsilon = 2$ even at large amounts of outlying charge disprove the assumption that SS(V)PE (and thus IEFPCM) would in any way be better in taking into account the outlying charge effects by some kind of approximate volume polarization term. The huge advantage of these methods over the classical DPCM just results from the elimination of the problematic normal electric field component from the boundary condition by making use of the conductor limit which was avoided from the beginning in the COSMO model.

All other parameters of continuum solvation methods, e.g., the choice of the construction method and radii for the cavities, the choice of the quantum chemical method and basis set, and the nonelectrostatic contributions, will have a much larger influence on the quality of continuum solvation calculations than the choice of the theoretically slightly better justified IEFPCM/SS(V)PE. Considering the facts that the entire dielectric continuum solvation concept is only a crude approximation to the situation in real solvents,[19] and that the currently best overall agreement between calculated and experimental solvation free energies is in the order of 0.5−1 kcal/mol (RMSD),[16,17] the small theoretical accuracy gain of ~0.07 kcal/mol (RMSD) of IEFPCM/SS(V)PE vs COSMO found in our benchmark lets the justification for the considerable additional algorithmic and computational expenses of the advanced methods appear questionable.

ASSOCIATED CONTENT

Supporting Information

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Names and geometries in xyz format of all used solutes in the data set (ZIP)

All calculated total energies are reported in Table SI1 (XLSX)

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Notes

The authors declare no competing financial interest.

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