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RESEARCH ARTICLE

A quick solvation energy estimator based on electronegativity equalization

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Abstract

ESE-EE (Easy Solvation Estimation with Electronegativity equalization) is a quick method for estimation of solvation-free energies $\Delta G^{o}_{\text{solv}}$, which uses a thoroughly fitted electronegativity equalization (EE) scheme to obtain atomic charges, which are further employed in a scaled noniterative COSMO-like calculation to evaluate the electrostatic component of $\Delta G^{o}_{\text{solv}}$. Nonelectrostatic corrections including adjustable parameters are also added. For neutral solutes, ESE-EE yields a mean absolute error (MAE) in $\Delta G_{\text{solv}}{}^{\circ}$ of 1.5 kcal/mol for *aqueous* solutions; 1.0 kcal/mol for nonaqueous *polar protic* solvents; 0.9 kcal/mol for *polar aprotic* solvents; and about 0.6 kcal/mol for *nonpolar* solvents. Since ESE-EE only requires a molecular geometry as input for a $\Delta G^{o}_{\text{solv}}$ prediction, it can be utilized for a rapid screening of $\Delta G^{o}_{\text{solv}}$for large neutral molecules. However, for ionic solutes, ESE-EE yields larger errors (typically several kcal/mol) and is recommendable for preliminary estimations only. Upon a special refitting, ESE-EE is able to yield partition coefficients with a good accuracy.

KEYWORDS
atomic charges, continuum solvation methods, electronegativity-equalization, solvation-free energies

1 | INTRODUCTION

In order to study processes in solutions, the solvation free energy $\Delta G^{o}_{\text{solv}}$ is routinely calculated by a variety of methods. Most used are the Continuum Solvation (CS) models that include the Polarizable Continuum Model (PCM)[1–9] and the Generalized Born (GB) method,[10,11] including SMx.[12–14] Usually, the computed $\Delta G^{o}_{\text{solv}}$ is expressed as a sum of the electrostatic energy E_{elst} and the correction term $\Delta G^{o}_{\text{corr}}$, which mainly describes nonelectrostatic effects:

$$\Delta G^{\cdot\cdot}{}_{\text{solv}} = E_{\text{elst}} + \Delta G^{\cdot\cdot}{}_{\text{corr}} \tag{1}$$

In the PCM family of methods, the solute placed in a cavity interacts with the solvent represented by a continuum with certain electrical properties. The polarization of the solvent by the solute is described by an electric charge distribution on the surface of the cavity. Among the most efficient PCM methods is the COSMO method developed by Klamt and Schüürmann,[15–19] and the closely related C-PCM.[20,21] In COSMO, E_{elst} is computed as interaction energy of either the electron density $\rho(\mathbf{r})$ and nuclear charges $\{Z_A\}$, or of atomic charges $\{Q_A\}$ of the solute with the induced charges $\{q_i\}$ located on the surface of the molecular cavity:

$$E_{\text{elst}} = \frac{1}{2}\left(1 - \frac{1}{\varepsilon}\right)\sum_i \sum_A \frac{Q_A q_i}{|\mathbf{R}_A - \mathbf{r}_i|} \tag{2}$$

where ε is the dielectric constant of the solvent. The induced charges $\{q_i\}$ in COSMO are obtained from atomic charges $\{Q_A\}$ by solving

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Dedicated to Professor Gernot Frenking on the occasion on his 75th birthday.

TABLE 1 Element- and coordination-number-dependent EE parameters optimized by nonlinear least square fitting

Element	Coordination number	A_i	B_i	Element	Coordination number	A_i	B_i
H	1	2.408	1.260	P	1	2.500	0.600
	2	2.295	1.463		2	2.500	0.600
C	1	2.489	0.699		3	2.477	0.607
	2	2.465	0.702		4	2.443	0.590
	3	2.541	0.814		5	2.500	0.600
	4	2.527	0.823	S	1	2.522	0.612
N	1	2.605	0.795		2	2.431	0.665
	2	2.595	0.796		3	2.398	0.659
	3	2.535	0.760		4	2.388	0.651
	4	2.573	0.909		5	2.44	0.665
O	1	2.505	0.839		6	2.44	0.665
	2	2.532	0.883	Cl	1	2.555	2.090
	3	2.609	1.091	Br	1	2.520	1.298
F	1	2.790	2.893	I	1	2.457	1.387
Si	3	2.300	0.600				
	4	2.322	0.605				

Note: $\kappa = 0.813$ Å; $\kappa_2 = 0.931$ Å.

TABLE 2 Van der Waals radii R_A^{vdW} (Å) and parameters ζ (kcal/mol·Å^{-3}), κ_A (kcal/mol·Å^{-2}), and g_A (kcal/mol) for main-group elements for various classes of solvents

	H	C	N	O	F	S	Cl	Br	I
R_A^{vdW}	0.815	1.321	2.01	1.814	1.59	1.8	1.989	1.85	1.98
Solvent class A—water $k = 1.153$; $\zeta = 0.0852$									
κ_A	−0.515	−0.162	−0.162	−0.145	−0.030	−0.134	−0.099	−0.122	−0.153
g_A	34.4	38.7	13.6	7.36	5.75	33.8	23.3	37.8	69.4
Solvent class A—water–special fitting[a] $k = 1.121$; $\zeta = 0.115$									
κ_A	−0.398	−0.160	−0.182	−0.207	−0.041	−0.159	−0.109	−0.148	−0.158
g_A	32.19	28.68	−0.31	7.03	−4.32	41.85	8.63	26.74	44.97
Solvent class B—polar protic $k = 1.093$; $\zeta = 0.0565$									
κ_A	−0.354	−0.151	−0.106	−0.161	−0.027	−0.122	−0.093	−0.140	−0.145
g_A	26.51	26.09	0.71	16.94	−1.19	30.43	18.18	32.91	38.48
Solvent class C—polar aprotic $k = 1.048$; $\zeta = 0.139$									
κ_A	−0.288	−0.256	−0.085	−0.192	−0.307	−0.137	−0.156	−0.149	
g_A	6.27	40.88	0.40	20.84	47.61	6.649	25.46	35.65	
Solvent class D—nonpolar $k = 0.391$; $\zeta = -0.146$									
κ_A	−0.054	0.0125	0.047	0.016	0.134	0.019	0.093	0.062	0.054
g_A	17.51	−2.23	1.12	5.64	−16.3	39.03	−13.73	−15.64	−14.83

Note: The ξ_{solv} values are given in the Supporting Information, Data S1.

[a] Parameters optimized for the water/octanol partition coefficient is described in the following sections.

a simple system of linear equations. In our previous papers,[22–24] we presented a noniterative yet quite accurate method, uESE (universal Easy Solvation Evaluation), for calculating solvation energies for both aqueous and nonaqueous solutions. It uses the COSMO electrostatics plus a number of additive correction terms that depend on atomic surface areas $\{S_A\}$, atomic surface charges $\{q_i\}$, and on the total cavity volume V. Within the uESE formalism, the atomic charges $\{Q_A\}$ can be calculated by a variety of methods,[22,25,26] but a particular charge scheme, CM5,[27] yields the best results. Recently, we proposed a variation of the uESE method, dubbed ESE-PM7,[28] in which the semiempirical PM7 method is used to compute $\{Q_A\}$. Albeit somewhat less accurate than the CM5-based uESE method, ESE-PM7 still provides quite reliable solvation energies: the mean absolute error (MAE) in $\Delta G^{o}_{\mathrm{solv}}$ for neutral solutes varies from

TABLE 3 Mean signed error (MSE), mean absolute error (MAE), and the SD of the hydration-free energy in kcal/mol for various datasets by the ESE-EE method with respect to reference values in comparison with the ESE-PM7 and PM7/COSMO2 method

	ESE-PM7			ESE-EE			PM7/COSMO2
Solute set (number of entries)[a]	**MSE**	**MAE**	**SD**	**MSE**	**MAE**	**SD**	**SD**
MNSol(528)[b]	0.19	2.00	2.79	−0.06	2.37	3.34	
Neutrals(389)	−0.04	1.62	2.21	−0.07	1.53	2.04	
Cations(59)	1.25	3.13	3.91	0.35	4.15	5.09	
Anions(80)	0.52	3.01	4.03	0.24	4.36	5.41	
MNSol*(464)[c]	0.35	1.91	2.64	0.03	2.32	3.31	2.62[d]
Neutrals(330)	0.08	1.46	1.90	−0.13	1.70	2.29	2.24[d]
Cations(59)	1.25	3.13	3.91	0.35	4.15	5.09	2.87[d]
Anions(75)	0.86	2.91	3.91	0.01	4.34	5.38	3.69[d]
Mobley141(141)[c]	−0.43	1.25	1.72	0.08	1.64	2.22	2.54[e]
Blind(63)[c]	−0.83	2.53	3.49	−0.49	2.69	3.42	
SAMPL1(53)[c]	−0.24	2.35	3.50	0.01	2.36	2.96	3.73[d]
SAMPL4(42)[c]	−0.29	1.28	1.60	−0.33	1.85	2.42	1.92[d]
C10(10)[c]	1.00	1.65	2.22	0.06	6.18	6.87	2.28[d]

[a] The complete lists of solutes and the calculated hydration-free energies and the reference values are given in the Supporting Information, Data S1.
[b] Fitting set; for explanation see text.
[c] Testing set; for explanation see text.
[d] Data from reference [45].
[e] Data from reference [45], "Mobley266" dataset.

TABLE 4 MSE, MAE, and SD of the hydration free energy in kcal/mol for various subset of neutral molecules calculated by the ESE-EE method

Subsets (number of entries)	MSE	MAE	SD
Small molecules(24)[a]	−1.26	1.74	2.42
Alcohols(18)	1.35	1.35	1.50
Aldehydes and Ketones(22)	1.18	1.20	1.44
Ethers(10)	−1.17	1.17	1.28
Esters(21)	−1.06	1.57	1.64
Acids(10)	1.06	1.06	1.21
Amines(42)	0.02	1.10	1.37
Nitriles(4)	−1.06	1.06	1.22
Nitro compounds and nitrates(17)	−2.65	2.65	3.03
Fluorine compounds(33)	−0.56	1.85	2.57
Chlorine compounds(74)	0.26	1.73	2.38
Bromine compounds(25)	0.40	1.55	2.04

[a] Less than six atoms.

TABLE 5 MAE of the hydration-free energy in kcal/mol for various datasets by the ESE-EE method with respect to reference values in comparison with the uESE, SMD, and SMD/PM3 methods

Solutes[a]	SMD/DFT	uESE/DFT	SMD/PM3	ESE-EE
MNSol(528)	2.53	1.47[b]	2.3[c]	2.37
Neutrals(389)	1.15[d]	0.99[b]	1.5[c]	1.53
Cations(59)	3.76[d]	2.73[b]	5.5[c]	4.15
Anions(80)	8.92[d]	2.83[b]	3.2[c]	4.36

[a] The complete lists of solutes and the calculated hydration-free energies and the reference values are given in the Supporting Information, Data S1.
[b] Data from reference [24].
[c] Data from reference [49] (table III).
[d] Data from reference [23].

0.5 kcal/mol for nonpolar solvents to 1.6 kcal/mol for water and is about 3.1 kcal/mol for ions in water. On the other hand, ESE-PM7 has a huge advantage over DFT-based methods in terms of computational speed.

All the methods of the ESE family has some degree of empiricism, as do many PCM[13,29] and GB[10,12,30] models. In the DFT-based uESE versions,[22–24] a number of adjustable parameters are included in the $\Delta G^{o}_{\text{corr}}$ term, while the COSMO electrostatic term is calculated as is with standard Bondi[31] van der Waals radii employed for the cavity construction. In the ESE-PM7 method,[28] van der Waals radii were additionally optimized. The correction term in the ESE-PM7 method[28] is as follows:

$$\Delta G^{\circ}_{\text{corr}} = \sum_A \left[(\xi_{\text{solv}} + \kappa_A) S_A + g_A q_A \right] + \zeta V \tag{3}$$

where κ_A and g_A are element-dependent adjustable parameters; ξ_{solv} is an optional solvent-dependent shift parameter; ζ is a global parameter. The physical meaning of these terms was discussed previously.[22–24,28]

The fact that quite different atomic-charge schemes can produce charges suitable for a uESE-like COSMO-based solvation energy method, allows for application of another, possibly simpler (hence quicker) charge scheme. In this paper, we propose using electronegativity-equalization (EE) charges for calculation of solvation free energies.

Although the EE concept is based on quantum-mechanical considerations,[32–35] in particular on the density functional theory (DFT), practical calculation of EE charges does not require any

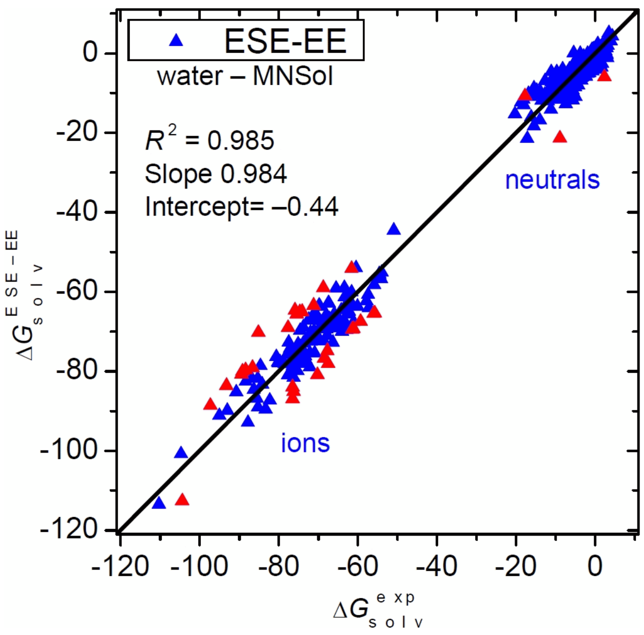


FIGURE 1 Hydration-free energies (in kcal/mol) for 528 molecules and ions calculated by ESE-EE method for the MNSol dataset versus experimental values. Red points denote failures ($|\Delta^{calc}G^{\circ}_{solv} - \Delta^{ref}G^{\circ}_{solv}| > 7$ kcal/mol).

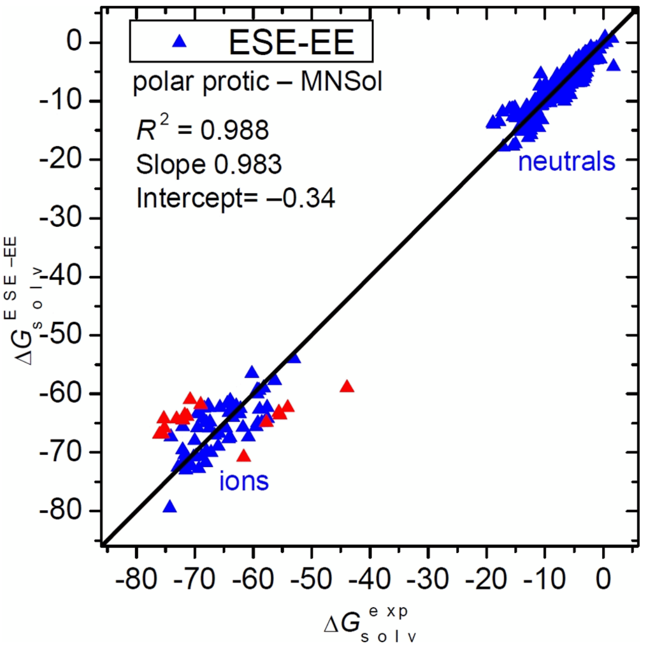


FIGURE 2 Solvation-free energies (in kcal/mol) in nonaqueous polar protic solvents (class **B**) for 467 molecules and ions calculated by our ESE-EE method versus experimental values. Red points denote outliers with a deviation greater than 7 kcal/mol.

TABLE 6 MSE, MAE, and SD of the solvation-free energy in kcal/mol for 14 *polar protic* solvents computed using the ESE-EE model in comparison with uESE-CM5 and SMD (a total of 467 entries)

	uESE-CM5[b]	SMD[b]	ESE-PM7	ESE-EE		
Solvent[a]	MAE	MAE	MAE	MSE	MAE	SD
Octanol(247)	0.75	1.24	1.02	−0.12	1.18	1.61
Heptanol(12)	0.47	0.74	0.85	0.03	0.71	0.88
m-Cresol(7)	0.68	1.56	1.13	0.55	1.16	1.37
Benzyl alcohol(10)	0.35	0.66	0.67	−0.11	0.54	0.79
Hexanol(14)	0.44	0.77	0.82	−0.06	0.64	0.78
Pentanol(22)	0.66	0.72	0.97	−0.27	0.84	1.11
sec-Butanol(9)	0.44	0.53	0.39	−0.18	0.44	0.58
Isobutanol(17)	0.63	0.56	0.75	−0.28	0.62	0.72
Methoxyethanol(6)	0.44	0.83	0.99	−0.34	0.45	0.75
Butanol(21)	0.68	0.64	0.94	0.05	0.89	1.40
Isopropanol(7)	0.63	1.02	1.03	−0.44	0.80	1.17
Propanol(7)	0.57	0.81	0.99	−0.36	0.82	1.15
Ethanol(8)	0.82	1.29	1.33	−1.01	1.21	1.60
Methanol—cations(29)	2.77	2.44	2.18	0.93	5.77	6.49
Methanol—anions(51)	1.73	3.70	1.69	−0.19	3.21	4.38
Methanol—all ions(80)	2.13	3.24	1.87	0.22	4.14	5.25
All polar protic solvents(467)	0.93	1.44	1.13	−0.08	1.56	2.54

[a] The number of entries in the dataset is given in parentheses.
[b] Data from reference [24].

TABLE 7 MSE and MAE of the solvation-free energy in kcal/mol for 20 *polar aprotic* solvents computed using the ESE-EE model in comparison with uESE-CM5 and SMD (a total of 338 entries)

Solvent[a]	uESE-CM5[b] MAE	SMD[b] MAE	ESE-PM7 MAE	ESE-EE MSE	ESE-EE MAE	ESE-EE SD
Bromoethane(7)	0.61	0.80	0.72	−0.13	1.25	1.43
2-Methylpyridine(6)	0.53	0.60	0.54	−0.12	0.88	1.12
o-Dichlorobenzene(11)	0.41	0.85	0.80	−0.19	1.06	1.24
Dichloroethane(39)	0.51	0.49	0.57	−0.13	1.09	1.32
4-Methyl-2-pentanone(13)	1.01	0.77	0.94	0.06	1.01	1.30
Pyridine(7)	0.48	0.65	0.61	−0.12	0.83	1.02
Cyclohexanone(10)	1.05	0.96	0.88	0.02	0.79	1.05
Acetophenone(9)	0.69	0.61	0.58	−0.03	0.72	0.94
Butanone(13)	0.81	0.96	0.90	−0.17	0.72	1.01
Benzonitrile(7)	0.56	0.77	0.82	−0.10	0.69	0.88
o-Nitrotoluene(6)	0.16	0.51	0.41	−0.10	0.62	0.69
Nitroethane(7)	0.30	0.58	0.68	−0.08	0.57	0.80
Nitrobenzene(15)	0.22	0.62	0.54	−0.10	0.71	0.85
Acetonitrile						
Neutral solutes(7)	0.69	0.74	0.92	−0.88	1.05	1.35
Cations(39)	2.01	7.93	2.41	0.60	5.13	6.17
Anions(30)	1.82	3.01	1.60	−0.57	3.03	3.87
All ions(69)	1.97	5.79	2.06	0.09	4.21	5.30
Nitromethane(7)	0.53	0.85	0.78	−0.03	0.66	0.87
Dimethyl formamide(7)	0.49	0.65	0.67	0.00	0.56	0.84
Dimethyl acetamide(7)	0.54	0.76	0.64	−0.01	0.60	0.87
Sulfolane(7)	0.54	1.48	0.86	0.00	0.68	1.03
Dimethyl sulfoxide (DMSO)						
Neutral solutes(7)	0.75	0.88	1.62	0.37	1.21	1.90
Cations(4)	2.25	8.31	1.85	2.97	5.37	5.78
Anions(66)	2.01	3.55	3.00	−1.41	5.20	6.37
Methyl formamide(7)	0.85	0.86	0.96	0.11	1.12	1.73
Polar aprotic neutrals(199)	0.59	0.73	0.74	−0.09	0.88	1.17
Cations(43)	2.03	7.96	2.36	0.82	5.15	6.14
Anions(96)	1.95	3.38	2.57	−1.15	4.53	5.71
All polar aprotic(338)	1.16	2.40	1.47	−0.28	2.47	3.86

[a] The number of entries in the dataset is given in parentheses.

[b] Data from reference 24.

quantum-mechanical input. A convenient computational form of EE charges can be expressed in matrix form as follows[35,36]:

$$\begin{pmatrix} B_1 & Y_{12} & \cdots & Y_{1N} & -1 \\ Y_{21} & B_2 & \cdots & Y_{2N} & -1 \\ \vdots & \vdots & \ddots & \vdots & \vdots \\ Y_{N1} & Y_{N2} & \cdots & B_N & -1 \\ 1 & 1 & \cdots & 1 & 0 \end{pmatrix} \begin{pmatrix} Q_1 \\ Q_2 \\ \vdots \\ Q_N \\ \overline{\chi} \end{pmatrix} = \begin{pmatrix} -A_1 \\ -A_2 \\ \vdots \\ -A_N \\ Q_{\text{tot}} \end{pmatrix} \tag{4}$$

Here B_i and A_i are element-dependent parameters characterizing the intrinsic electronegativity and hardness of ith atom, respectively; Q_{tot} is the total charge of the molecule; $\{Q_A\}$ are the resulting atomic charges obtained as the solution to the system of Equations (4); χ is the resulting equalized electronegativity. The off-diagonal matrix elements Y_{ik} depend on molecular geometry and it is through them only that structural information enters the EE equations. In the simplest version, Y_{ik} is merely the inverse interatomic distance $1/R_{ik}$, although other formulations have been proposed too.[36–39] B_i and A_i can be considered as adjustable parameters of a given EE charge scheme and do not need to correspond to an established electronegativity system. The distance-dependent off-diagonal terms Y_{ik} can also contain adjustable parameters if needed. The fitting of $\{A_i\}$ and $\{B_i\}$ and, if applicable, other parameters can be done using a reputable charge scheme[35–37,39] such as Mulliken[35,36] or CM1[37] charges as a reference.

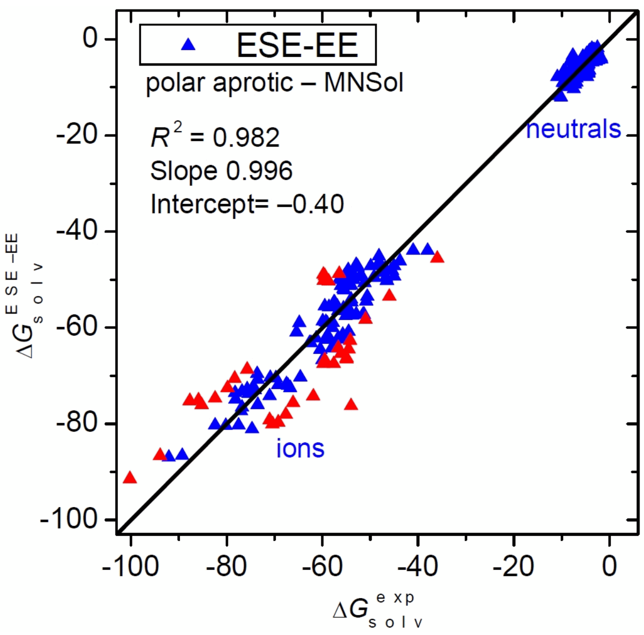


FIGURE 3 Solvation-free energies (in kcal/mol) in polar aprotic solvents (class **C**) for 339 molecules and ions calculated by the ESE-EE method versus experimental values. Red points denote outliers with a deviation greater than 4 kcal/mol.

The idea of the present work is to combine a properly parameterized EE-based charge scheme with an ESE-like solvation method. Since a calculation of EE charges does not require quantum-mechanical input and is equivalent to a solution of a small system of linear equtaions (Equation (4)) and the ESE formalism is fast due to its noniterative character, in this way, we aim to create a rapid solvation energy estimator, albeit not necessarily as accurate as the DFT-based uESE-CM5.[24]

2 | METHOD

The total solvation-free energy in the present ESE-EE method is a combination of the *scaled* COSMO electrostatic term E_{elst} and the correction term $\Delta G^{o}_{\text{corr}}$:

$$\Delta G^{\circ}_{\text{solv}} = k(1-1/\varepsilon)E_{\text{elst}} + \Delta G^{\circ}_{\text{corr}} \tag{5}$$

$$\Delta G^{\circ}_{\text{corr}} = \sum\nolimits_A [(\xi_{\text{solv}} + \kappa_A)S_A + g_A|q_A|] + \zeta V \tag{6}$$

with ξ_{solv}, $\{\kappa_A\}$, $\{g_A\}$, and ζ as adjustable parameters. Thus, instead of a quadratic $\sum_A p_A q_A{}^2$ in uESE[24] or linear $\sum_A g_A q_A$ term (Equation (3)) in the ESE-PM7 method,[28] the absolute value of the surface charge $|q_A|$ is employed in the present ESE-EE scheme (Equation (6)). The solvent-

TABLE 8 MSE and MAE of the solvation-free energy in kcal/mol for nonpolar solvents (class **D**) computed using the ESE-EE model in comparison with uESE-CM5 and SMD (a total of 1554 entries)

Solvent[a]	uESE-CM5 MAE	SMD[b] MAE	ESE-PM7 MAE	ESE-EE MSE	ESE-EE MAE	ESE-EE SD
Pentane(26)	0.28	0.35	0.34	−0.06	0.35	0.43
Hexane(59)	0.36	0.52	0.48	0.03	0.68	0.86
Heptane(69)	0.37	0.55	0.42	0.02	0.58	0.75
Isooctane(32)	0.39	0.45	0.39	0.00	0.48	0.61
Octane(38)	0.28	0.43	0.36	−0.05	0.38	0.50
Nonane(26)	0.22	0.37	0.18	−0.07	0.32	0.39
Decane(39)	0.30	0.43	0.29	−0.07	0.42	0.57
Undecane(13)	0.33	0.49	0.40	0.02	0.46	0.56
Dodecane(8)	0.34	0.30	0.18	−0.11	0.34	0.41
Cyclohexane(92)	0.46	0.60	0.49	0.02	0.74	1.03
Perfluorobenzene(15)	0.36	0.56	0.38	0.01	0.33	0.40
Pentadecane(9)	0.31	0.48	0.13	−0.16	0.45	0.55
Hexadecane(198)	0.45	0.68	0.45	−0.11	0.68	0.95
Decalin(27)	0.30	0.67	0.37	0.00	0.36	0.52
Carbon tetrachloride(79)	0.35	0.53	0.45	−0.01	0.58	0.78
Isopropyltoluene(6)	0.22	0.49	0.15	−0.03	0.13	0.16
Mesitylene(7)	0.25	0.54	0.39	0.00	0.19	0.30
Tetrachloroethene(10)	0.26	0.74	0.18	−0.01	0.18	0.26
Benzene(75)	0.51	0.81	0.71	0.13	0.80	1.13
sec-Butylbenzene(5)	0.16	0.25	0.19	0.02	0.14	0.17
tert-Butylbenzene(14)	0.25	0.40	0.29	0.01	0.23	0.26

TABLE 8 (Continued)

Solvent[a]	uESE-CM5 MAE	SMD[b] MAE	ESE-PM7 MAE	ESE-EE MSE	 MAE	 SD
Butylbenzene(10)	0.26	0.50	0.32	0.01	0.24	0.27
Trimethylbenzene(11)	0.21	0.46	0.20	0.01	0.31	0.32
Isopropylbenzene(19)	0.25	0.39	0.28	−0.08	0.39	0.59
Toluene(51)	0.30	0.58	0.39	−0.06	0.44	0.58
Triethylamine(7)	0.58	0.98	0.60	0.03	0.54	0.70
Xylene(48)	0.34	0.60	0.39	−0.02	0.39	0.51
Ethylbenzene(29)	0.30	0.47	0.35	−0.08	0.34	0.49
Carbon disulfide(15)	0.43	0.65	0.71	−0.10	0.66	0.85
Tetralin(9)	0.71	1.30	0.71	−0.31	0.74	1.19
Dibutyl ether(15)	0.60	0.79	0.58	0.06	0.41	0.50
Diisopropyl ether(22)	0.91	0.76	1.00	0.00	0.73	0.85
Hexadecyl iodide(9)	0.23	0.42	0.17	0.01	0.48	0.60
Phenyl ether(6)	0.35	1.05	0.48	0.11	0.56	0.66
Fluoroctane(6)	0.06	0.48	0.14	0.01	0.10	0.12
Ethoxybenzene(7)	0.34	0.45	0.47	0.09	0.50	0.59
Anisole(8)	0.27	0.51	0.46	0.11	0.55	0.67
Diethyl ether(72)	0.78	0.82	0.89	−0.02	0.99	1.30
Bromoform(12)	0.24	0.72	0.26	0.02	0.23	0.28
Iodobenzene(20)	0.45	0.34	0.50	0.02	0.36	0.47
Chloroform(109)	0.64	0.79	0.81	0.07	0.98	1.31
Dibromoethane(10)	0.34	0.70	0.34	0.00	0.17	0.21
Butyl acetate(22)	0.56	1.15	0.66	0.13	0.68	0.79
Bromooctane(5)	0.16	0.88	0.27	0.01	0.08	0.10
Bromobenzene(27)	0.39	0.51	0.51	0.02	0.30	0.38
Fluorobenzene(7)	0.51	0.83	0.69	0.11	0.55	0.67
Chlorobenzene(38)	0.39	0.65	0.47	−0.02	0.37	0.51
Chlorohexane(11)	0.17	1.10	0.30	0.03	0.23	0.27
Ethyl acetate(24)	0.85	1.10	0.97	0.07	1.19	1.59
Acetic acid(7)	0.46	2.37	0.73	0.29	1.21	1.46
Aniline(10)	0.70	0.78	0.84	0.34	1.22	1.54
Dimethylpyridine(6)	0.59	0.69	0.52	0.21	0.86	1.06
Tetrahydrofuran(7)	0.58	0.77	0.72	0.17	0.62	0.81
Decanol(11)	0.62	1.22	0.91	0.06	0.61	0.71
Tributyl phosphate(16)	0.54	0.56	0.43	0.12	0.81	0.89
Nonanol(10)	0.83	0.73	1.33	−0.05	1.00	1.22
Dichloromethane(11)	0.67	0.65	0.83	0.05	0.63	0.77
All non-polar (1554)	0.44	0.65	0.51	0.00	0.60	0.87

[a] The number of entries in the dataset is given in parentheses.
[b] Data from reference [24].

dependent shift parameters ξ_{solv} apply to aprotic and nonpolar solvents only. The COSMO electrostatic term is scaled, with the scaling factor k being an extra adjustable parameter. Otherwise, the COSMO version implemented in ESE-EE is identical to that we used in ESE-PM7.[28] The atomic radii employed for the van der Waals cavity construction are also adjustable parameters of the method, the same way as they are in ESE-PM7.[28]

The calculation of the COSMO electrostatic term E_{elst} in ESE-EE is virtually identical to that in our recent works,[24,28] except that the EE atomic charges $\{Q_A\}$ are evaluated by solving the system of linear equations (Equation (4)), where $\{A_i\}$ and $\{B_i\}$ are adjustable parameters that are individual for each element and coordination number of each atom. This approach is similar to that of Svobodová Vařeková et al.,[36] and Ouyang et al.[40] who used hybridization-specific parameters $\{A_i\}$ and $\{B_i\}$. However, calculation of atomic coordination number is simpler and more efficient than determination of hybridizations. The distance-dependent off-diagonal matrix elements Y_{ik} contain two more parameters κ and κ_2:

$$Y_{ik}=\frac{\kappa}{R_{ik}+\kappa_2/(B_i+B_k)^2} \tag{7}$$

This form of Y_{ik} is inspired by but not identical to those used by Nalewajski et al.[41] and Menegon et al.[37]

The solvents are split into four classes: (**A**) water; (**B**) nonaqueous polar protic; (**C**) polar aprotic; and (**D**) nonpolar solvents, as was done in our recent works.[24,28]

Nonlinear least-square fitting of the EE parameters $\{A_i\}$, $\{B_i\}$, κ, and κ_2 as well as the van der Waals radii was carried out using the downhill simplex algorithm[42] available in the Python SciPy package,[43] which does not requires analytical derivatives. The resulting values of the EE parameters are provided in Table 1. Within this fitting, for any given set of the EE parameters, the parameters k, $\{\kappa_A\}$, $\{g_A\}$, and ζ were fitted using the *linear* least-square method first for aqueous solutions. Subsequently, with EE parameters and van der Waals radii unchanged, the parameters k, $\{\kappa_A\}$, $\{g_A\}$, and ζ were refitted and tested separately for the four classes of solvents, as described previously.[28] Finally, the solvent-dependent parameter ξ_{solv} was found for each aprotic or nonpolar solvent by a separate least-squares fit.

As a reference, ΔG^o_{solv} values from the Minnesota Solvation Database[44] were used. The final values of parameters k, $\{\kappa_A\}$, $\{g_A\}$, and ζ for each of the solvent classes **A**–**D** are given in Table 2. The solvent-dependent parameters ξ_{solv} for classes **C** and **D** are listed in the Supporting Information, Data S1.

3 | RESULTS AND DISCUSSION

The ESE-EE method was fitted as described in the Section 2 using the solvation-free energies from the Minnesota Solvation Database ("MNSol")[44] as a reference. The method testing was performed using a number of datasets that we employed in our previous work[28] on the ESE-PM7 method. These are the following: the 464-solute dataset by Kříž and Řezáč[45] (MNSol*); the 141-solute subset from the Mobley et al.'s dataset[46] ("Mobley"); the 63 neutral-solute "Blind" dataset by Guthrie[47]; the 53-molecule ("SAMPL1") reduced Guthrie's dataset[47] used by Kříž and Řezáč[45]; reduced Guthrie's SAMPL4 dataset[48]; the ionic "C10" dataset.[45]

3.1 | Aqueous solutions

The results given in Table 3 indicate somewhat larger overall errors for the ESE-EE method than for ESE-PM7, although the problems mostly come from ions. In contrast, for neutral molecules from the MNSol fitting set ESE-EE performs even slightly better than ESE-PM7 both in terms of the mean absolute error (MAE) and the standard deviation (SD; root-mean-square error). For the MNSol* and Mobley141 testing sets, the ESE-EE method no

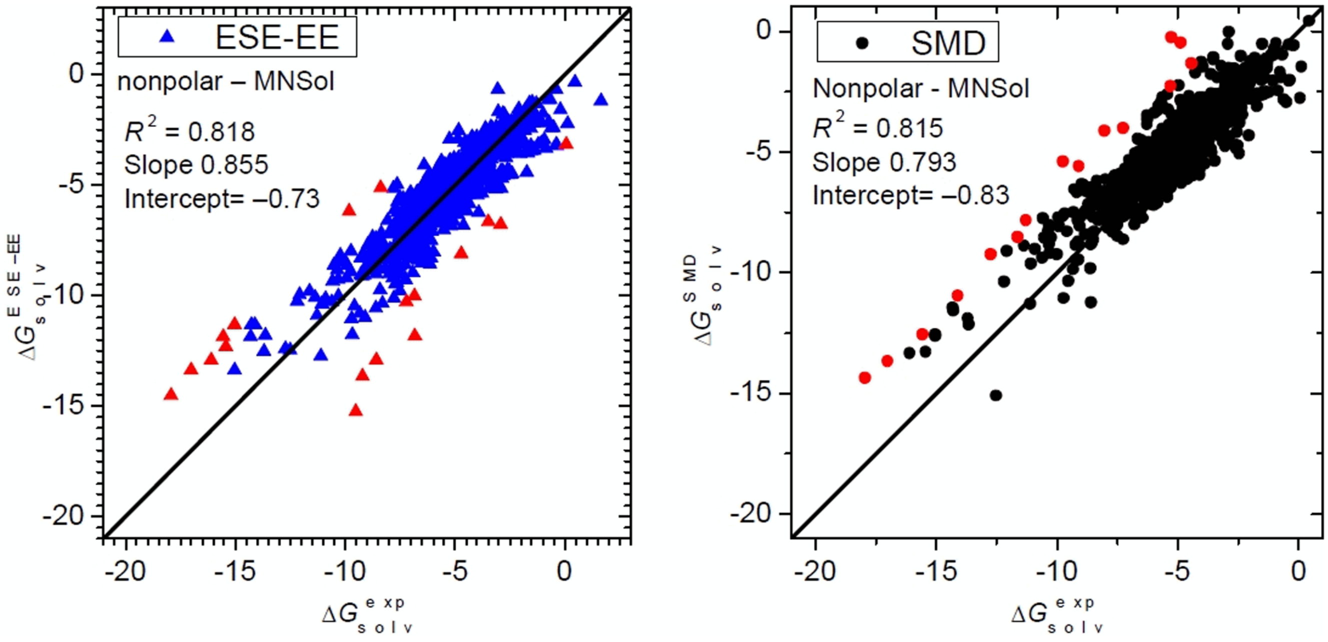
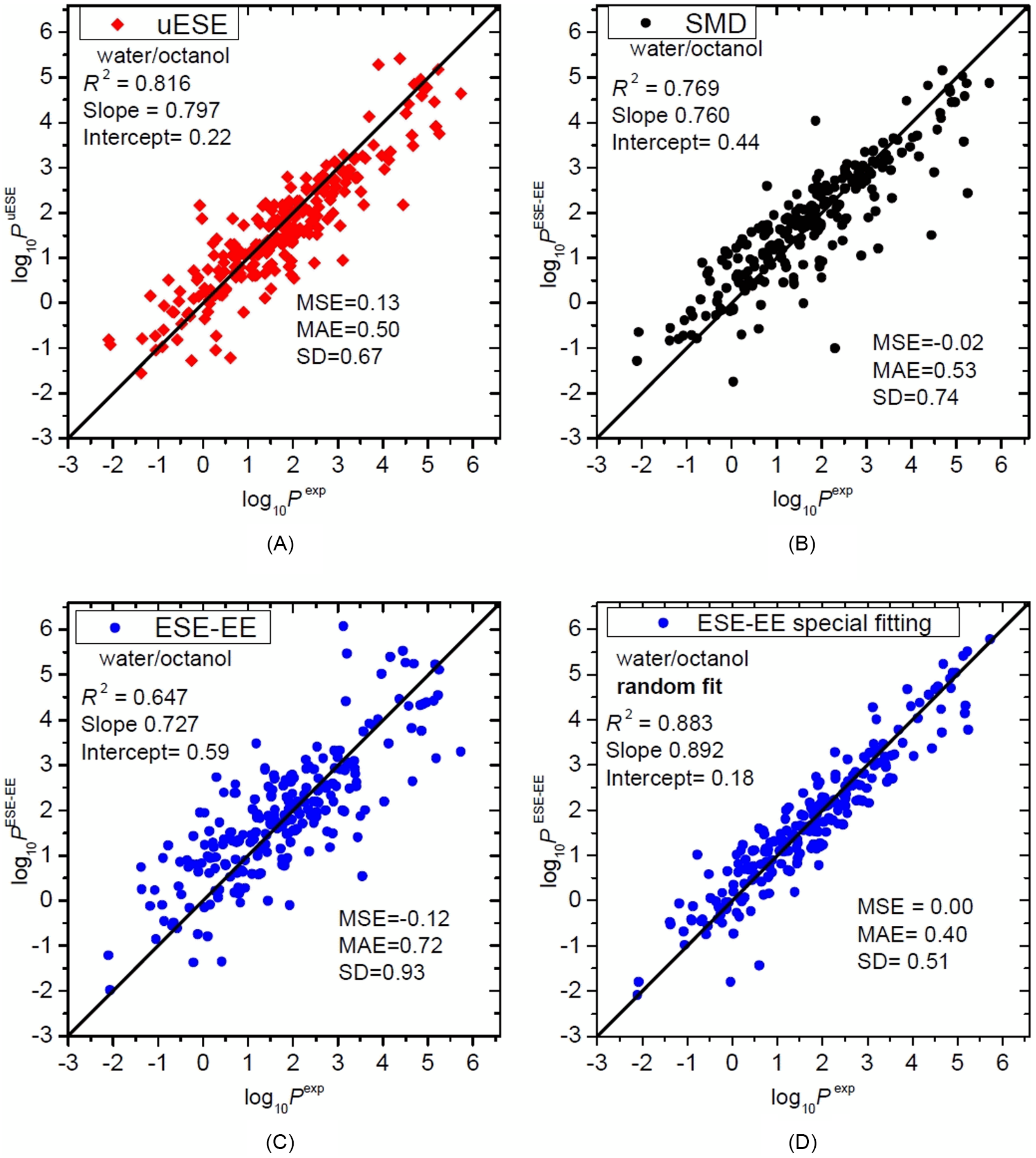


FIGURE 4 Solvation free energies (in kcal/mol) in nonpolar solvents (class **D**) for 1554 molecules calculated by the ESE-EE method versus experimental values. Red points denote outliers with a deviation greater than 3 kcal/mol. SMD results are given for comparison.



(A) (B) (C) (D)

FIGURE 5 Water/octanol partition coefficients obtained by uESE (A), SMD (B), ESE-EE with standard parameters (C), and ESE-EE with re-fitted parameters (D) versus experimental values.

longer holds the advantage. Nevertheless, for the “Blind” dataset, the performance of ESE-EE and ESE-PM7 is similar (slightly in favor of ESE-PM7 in terms of MAE and in favor of ESE-EE in terms of SD). For the SAMPL1 dataset, ESE-ESE works much better in terms of SD, while the situation is reversed in the case of the SAMPL4 set. Data given in Table 4 indicate that ESE-EE performs somewhat better for alcohols, aldehydes, ketones, ethers, carboxylic acids, nitriles, and amines. Its performance is poorer than average for halogen-containing solutes, nitro compounds, and nitrates.

The ESE-EE method is less reliable for ionic subsets, in which case the SD is typically >1 kcal/mol greater than that of the ESE-PM7 method.

A comparison of ESE-EE hydration energies to those obtained with other solvation methods is given in Table 5. Compared to the DFT-based uESE method for the MNSol testing set,[24] the MAE of ESE-EE is 0.9 kcal/mol larger, but with respect to SMD/DFT,[13] ESE-EE turns out even slightly more accurate. This advantage is mainly owing to large errors (an MAE up to 9 kcal/mol) of the SMD method for ionic solutes. For the neutrals, SMD/DFT is more accurate, while SMD/PM3[49] (which is still a quantum-chemically based method) has about the same accuracy as ESE-EE.

Individual hydration energies calculated by the ESE-EE method are visualized in Figure 1, with outliers indicated in red. While there are just three problematic neutral cases (dihydrogen, 1,4,5,8-tetraaminoanthraquinon [“test1060”], and 5-chlorouracil [“n202”]), 28 ions exhibit errors greater than 7 kcal/mol. In the case of dihydrogen, the atomic charges are zero due to symmetry, and the calculated COSMO electrostatic energy will be zero as well. Tetraaminoanthraquinon and chlorouracil feature strong hydrogen bonds that can lead to an incorrect description of solute-solvent interactions. On the whole, we observe that the ESE-EE method provides fairly reliable estimates of hydration energies for neutral solutes, but has a larger error for ions.

3.2 | Nonaqueous solutions

The solvation-free energies evaluated by the ESE-EE method for nonaqueous *polar protic* solvents (solvent class **B**) are compared to uESE-CM5, uESE-PM7, and SMD methods in Table 6. For neutral solutes ESE-EE exhibits a convincing performance, giving a lower MAE than uESE-PM7 for 10 solvents and lower than the (DFT-based) SMD for 9 solvents out of 14, although the DFT-based uESE-CM5 method is still better. Nevertheless, the MAE of ESE-EE is below 1 kcal/mol, with no case of a substantial failure for the neutral solutes, as can be seen in Figure 2. Computed for all the neutral solutes, the MAE is 1.03 kcal/mol. However, for ions, in particular for cations, ESE-EE has a more substantial error.

For *polar aprotic* solvents (class **C**, see Table 7 and Figure 3) the new ESE-EE methods exhibits an overall performance close to that of the standard SMD method, with an MAE of about 2.5 kcal/mol. For 14 out of 20 solvents, the MAE of the ESE-EE method is within 1 kcal/mol, and for the others is within 1.25 kcal/mol. ESE-EE is superior to SMD for nine of the class-C solvents. At average, for all the neutral solutes, an MAE of the ESE-EE of about 0.9 kcal/mol method is convincingly small. However, for ions, in particular for cations, ESE-EE is again considerably less accurate than for neutral solutes, and is also inferior to the SMD and ESE-PM7. The worst case in the cyanide ion (“i046”) in DMSO with a deviation of 22.3 kcal/mol, which is also problematic in the aqueous solution, though not so dramatically (with a deviation of 10.6 kcal/mol), despite the EE charges in CN^- are quite similar to the CM5 ones. Note that CN^- in DMSO is a difficult case also for SMD, which yields a deviation of 12.8 kcal/mol and uESE-PM7 (a deviation of 11.0 kcal/mol), but less so for uESE-CM5 (a deviation of 5.0 kcal/mol).

Table 8 presents statistical data for nonpolar solvents (class **D**). On the whole, the ESE-EE method exhibits a convincing accuracy, with an MAE of 0.6 kcal/mol, which is even slightly lower than that of the SMD method, though slightly larger than that of the uESE-CM5 and uESE-PM7 method. ESE-EE turns out to be superior to SMD for 35 of 57 solvents and is better than ESE-PM7 for 24 solvents studied.

Individual solvation energies in nonpolar solvents computed at ESE-EE and SMD levels are summarized in Figure 4. ESE-EE shows about the same R^2 value as SMD and a better slope and intercept. There are 18 deviating data (an error greater than 3 kcal/mol) for ESE-EE, the worst cases being dimethyl-4-nitrophenylthiophosphate (“0441pho”, an error 5.7 kcal/mol) in chloroform and 3,5-dibromo-4-hydroxybenzonitrile (“0425dbr,” an error of 5 kcal/mol) in cyclohexane, both are relatively polar nitrogen-containing species. The standard DFT-based SMD method exhibits a slightly smaller yet comparable number of outliers (15 data with an error >3 kcal/mol), with diiodomethane (“test4002”, an error of 5.0 kcal/mol) in hexadecane as the worst case.

3.3 | Partition coefficients

Solvation free energies can be employed to calculate a partition coefficient P of a solute between two solvents S_1 and S_2 according to the formula: $P = \exp((\Delta G^o_{\mathrm{solv}}(S_1) - \Delta G^o_{\mathrm{solv}}(S_2))/RT)$. To estimate the reliability of various solvation methods in this context, water/octanol partition coefficients were calculated for 234 entries available in the Minnesota Solvation Database[44] using the uESE, SMD, and ESE-EE methods. The results are represented graphically on logarithmic scale in Figure 5. While uESE and, to lesser extent, SMD perform reasonably well, ESE-EE gives deviation in a large number of cases. This is because ESE-EE is better for octanol than for water, leading to a bias in the $\Delta G^o_{\mathrm{solv}}(\mathrm{water}) - \Delta G^o_{\mathrm{solv}}(\mathrm{octanol})$ evaluation. Therefore, we decided to refit the ESE-EE parameters for aqueous solutions. To this end, the 234-dataset was split randomly into a fitting and testing subsets of 117 entries each. Using the fitting subset, the parameters k, $\{\kappa_A\}$, $\{g_A\}$, and ζ (Equation (6)) were refitted by minimizing the SD of $\log_{10}P_{\mathrm{water/octanol}}$. The new parameters are given in Table 2 under the entry “special fitting.” As shown in Figure 5D, the new parameters allow obtaining reliable partition coefficient, overrunning in quality even the uESE method. This is because such a refitting takes advantage of an error compensation between $\Delta G_{\mathrm{solv}}{}^\circ(\mathrm{water})$ and $\Delta G_{\mathrm{solv}}{}^\circ(\mathrm{octanol})$. As a result, $P_{\mathrm{water/octanol}}$ can be obtained more accurately than individual $\Delta G_{\mathrm{solv}}{}^\circ(\mathrm{water})$ and $\Delta G_{\mathrm{solv}}{}^\circ(\mathrm{octanol})$.[50]

4 | CONCLUSIONS

The author presents an extraordinarily simple method, ESE-EE, of estimation solvation-free energies of neutrals molecules and ions that requires molecular geometries only, without invoking any quantumchemical information as input. The methods is based on EE atomic charges, from which the electrostatic component of ΔG^o_{solv} is calculated using a noniterative version of the COSMO method. Nonelectrostatic adjustable corrections depending on atomic surface areas, surface charges, and on the total cavity volume are added. The parameters of the EE method, as well as van der Waals radii are also adjustable parameters of ESE-EE. The method was fitted and tested on a large number of solutes for a total of 92 solvents. The MAE of the ESE-EE method in aqueous solutions is found to be 1.53 kcal/mol for neutral solutes and 4.3 kcal/mol for ions. The performance for neutrals in aqueous solutions is very similar to that of semiempirical-based solvation methods such as ESE-PM7[24] or PM7/COSMO2,[45] while the ESE-EE method is still not as accurate as major DFT-based approaches such as SMD or uESE. For hydrated ions, ESE-EE is substantially less reliable than for neutrals. For nonaqueous *polar protic* solvents, ESE-EE yields quite reliable ΔG^o_{solv} of neutral solutes and is comparable in accuracy with SMD, but also exhibits more substantial errors for ions. The performance of ESE-EE for *polar aprotic* solvents is quite similar to that of SMD, with an MAE of about 0.9 kcal/mol for neutral solutes and about 4.7 kcal/mol for ions. In the case nonpolar solvents (with only neutral solutes tested), the ESE-EE method produces a mean error even slightly below that of SMD.

In summary, ESE-EE can serve as a quick and reasonably reliable ΔG^o_{solv} standalone estimator for minimum-energy structures of neutral solutes in a wide range of solvents from scratch. It can be implemented in a very efficient way when combining the a sparse-matrix technique[51,52] for the EE equations with the ddCOSMO linear-scaling algorithm[53,54] for the COSMO equations. However, for ionic solutes ESE-EE is not accurate enough to allow for reliable truly quantitative predictions. It is also not recommendable for molecular geometries far away from their equilibrium configuration, since the charge distribution may not be described adequately by the EE method.

ESE-EE can be used to predict partition coefficients. To do it with a good accuracy, a parameter refitting is desirable.

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DATA AVAILABILITY STATEMENT

The Supporting Information is openly available: Parameters ξ_{solv} (Table S1); ESE-EE-calculated solvation free energies in various solvents (Tables S2–S15). Water/octanol partition coefficients calculated by various methods (Table S16); PM7-optimized molecular geometries and EE charges for all solutes (Table S17). The ESE-EE program executables will be available for download: http://iqc.udg.es/~vybo/ESE

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REFERENCES

[1] J. Tomasi, B. Mennucci, R. Cammi, *Chem. Rev.* **2005**, *105*, 2999.

[2] R. E. Skyner, J. L. McDonagh, C. R. Groom, T. van Mourik, J. B. O. Mitchell, *Phys. Chem. Chem. Phys.* **2015**, *17*, 6174.

[3] V. Barone, M. Cossi, J. Tomasi, *J. Chem. Phys.* **1997**, *107*, 3210.

[4] E. Cancès, B. Mennucci, J. Tomasi, *J. Chem. Phys.* **1997**, *107*, 3032.

[5] M. Cossi, N. Rega, G. Scalmani, V. Barone, *J. Chem. Phys.* **2001**, *114*, 5691.

[6] M. Cossi, G. Scalmani, N. Rega, V. Barone, *J. Chem. Phys.* **2002**, *117*, 43.

[7] F. Lipparini, G. Scalmani, B. Mennucci, E. Cancès, M. Caricato, M. J. Frisch, *J. Chem. Phys.* **2010**, *133*, 014106.

[8] A. Pomogaeva, D. M. Chipman, *J. Chem. Theory Comput.* **2014**, *10*, 211.

[9] A. Pomogaeva, D. M. Chipman, *J. Phys. Chem. A.* **2015**, *119*, 5173.

[10] W. C. Still, A. Tempczyk, R. C. Hawley, T. J. Hendrickson, *J. Am. Chem. Soc.* **1990**, *112*, 6127.

[11] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Chem. Theory Comput.* **2013**, *9*, 609.

[12] C. J. Cramer, D. G. Truhlar, *J. Am. Chem. Soc.* **1991**, *113*, 8305.

[13] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2009**, *113*, 6378.

[14] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Chem. Theory Comput.* **2013**, *9*, 3649.

[15] A. Klamt, G. Schüürmann, *J. Chem. Soc. Perkin Trans.* **1993**, *2*, 799.

[16] A. Klamt, COSMO and COSMO-RS. in *Encyclopedia of Computational Chemistry*, Vol. 1 (Ed: P. V. R. Schleyer), Wiley, Chichester, U.K **1998**, p. 604.

[17] A. Klamt, M. Diedenhofen, *J. Comput. Chem.* **2018**, *39*, 1648.

[18] J. Andzelm, C. Kölmel, A. Klamt, *J. Chem. Phys.* **1995**, *102*, 9312.

[19] A. Klamt, *WIREs Comput. Mol. Sci.* **2011**, *1*, 699.

[20] V. Barone, M. Cossi, *J. Phys. Chem. A* **1998**, *102*, 1995.

[21] M. Cossi, N. Rega, G. Scalmani, V. Barone, *J. Comput. Chem.* **2003**, *24*, 669.

[22] A. A. Voityuk, S. F. Vyboishchikov, *Phys. Chem. Chem. Phys.* **2019**, *21*, 18706.

[23] A. A. Voityuk, S. F. Vyboishchikov, *Phys. Chem. Chem. Phys.* **2020**, *22*, 14591.

[24] S. F. Vyboishchikov, A. A. Voityuk, *J. Comput. Chem.* **2021**, *42*, 1184.

[25] A. A. Voityuk, A. J. Stasyuk, S. F. Vyboishchikov, *Phys. Chem. Chem. Phys.* **2018**, *20*, 23328.

[26] S. F. Vyboishchikov, A. A. Voityuk, *J. Comput. Chem.* **2019**, *40*, 875.

[27] A. V. Marenich, S. V. Jerome, C. J. Cramer, D. G. Truhlar, *J. Chem. Theory Comput.* **2012**, *8*, 527.

[28] S. F. Vyboishchikov, A. A. Voityuk, *J. Chem. Inf. Model.* **2021**, *61*, 4544.

[29] C. Dupont, O. Andreussi, N. Marzari, *J. Chem. Phys.* **2013**, *139*, 214110.

[30] C. J. Cramer, D. G. Truhlar, SMx continuum models for condensed phases. in *Trends and Perspectives in Modern Computational Science*, Brill Academic Publishers, Leiden, The Netherlands **2011**, p. 112.

[31] A. Bondi, *J. Phys. Chem.* **1964**, *68*, 441.

[32] R. G. Parr, R. A. Donnelly, M. Levy, W. E. Palke, *J. Chem. Phys.* **1978**, *68*, 3801.

[33] W. J. Mortier, S. K. Ghosh, S. Shankar, *J. Am. Chem. Soc.* **1986**, *108*, 4315.

[34] P. Bultinck, W. Langenaeker, P. Lahorte, F. De Proft, P. Geerlings, C. Van Alsenoy, J. P. Tollenaere, *J. Phys. Chem. A* **2002**, *106*, 7895.

[35] P. Bultinck, W. Langenaeker, P. Lahorte, F. De Proft, P. Geerlings, M. Waroquier, J. P. Tollenaere, *J. Phys. Chem. A* **2002**, *106*, 7887.

[36] R. Svobodová Vařeková, Z. Jiroušková, J. Vaněk, Š. Suchomel, J. Koča, *Int. J. Mol. Sci.* **2007**, *8*, 572.

[37] G. Menegon, K. Shimizu, J. P. S. Farah, L. G. Dias, H. Chaimovich, *Phys. Chem. Chem. Phys.* **2002**, *4*, 5933.

[38] A. K. Rappé, W. A. Goddard III, *J. Phys. Chem.* **1991**, *95*, 3358.

[39] D. Bakowies, W. Thiel, *J. Comput. Chem.* **1996**, *17*, 87.

[40] Y. Ouyang, F. Ye, Y. Liang, *Phys. Chem. Chem. Phys.* **2009**, *11*, 6082.

[41] R. F. Nalewajski, J. Korchowiec, Z. Zhou, *Int. J. Quantum Chem.* **1988**, *S22*, 349.

[42] J. A. Nelder, R. Mead, *Computer J.* **1965**, *7*, 308.

[43] P. Virtanen, R. Gommers, T. E. Oliphant, M. Haberland, T. Reddy, D. Cournapeau, E. Burovski, P. Peterson, W. Weckesser, J. Bright, S. J. van der Walt, M. Brett, J. Wilson, K. J. Millman, N. Mayorov, A. R. J. Nelson, E. Jones, R. Kern, E. Larson, C. J. Carey, İ. Polat, Y. Feng, E. W. Moore, J. VanderPlas, D. Laxalde, J. Perktold, R. Cimrman, I. Henriksen, E. A. Quintero, C. R. Harris, A. M. Archibald, A. H. Ribeiro, F. Pedregosa, P. van Mulbregt, A. Vijaykumar, A. P. Bardelli, A. Rothberg, A. Hilboll, A. Kloeckner, A. Scopatz, A. Lee, A. Rokem, C. N. Woods, C. Fulton, C. Masson, C. Häggström, C. Fitzgerald, D. A. Nicholson, D. R. Hagen, D. V. Pasechnik, E. Olivetti, E. Martin, E. Wieser, F. Silva, F. Lenders, F. Wilhelm, G. Young, G. A. Price, G.-L. Ingold, G. E. Allen, G. R. Lee, H. Audren, I. Probst, J. P. Dietrich, J. Silterra, J. T. Webber, J. Slavič, J. Nothman, J. Buchner, J. Kulick, J. L. Schönberger, J. V. de Miranda Cardoso, J. Reimer, J. Harrington, J. L. Rodríguez Cano, J. Nunez-Iglesias, J. Kuczynski, K. Tritz, M. Thoma, M. Newville, M. Kümmerer, M. Bolingbroke, M. Tartre, M. Pak, N. J. Smith, N. Nowaczyk, N. Shebanov, O. Pavlyk, P. A. Brodtkorb, P. Lee, R. T. McGibbon, R. Feldbauer, S. Lewis, S. Tygier, S. Sievert, S. Vigna, S. Peterson, S. More, T. Pudlik, T. Oshima, T. J. Pingel, T. P. Robitaille, T. Spura, T. R. Jones, T. Cera, T. Leslie, T. Zito, T. Krauss, U. Upadhyay, Y. O. Halchenko, Y. Vázquez-Baeza, *Nat. Methods* **2020**, *17*, 261.

[44] A. V. Marenich, C. P. Kelly, J. D. Thompson, G. D. Hawkins, C. C. Chambers, D. J. Giesen, P. Winget, C. J. Cramer, D. G. Truhlar, Minnesota Solvation Database – version 2012, University of Minnesota, **2012**. https://conservancy.umn.edu/bitstream/handle/11299/213300/MNSolDatabase_v2012.zip (accessed: May 17, 2019).

[45] K. Kříž, J. Řezáč, *J. Chem. Inf. Model.* **2019**, *59*, 229.

[46] D. L. Mobley, K. A. Dill, J. D. Chodera, *J. Phys. Chem. B* **2008**, *112*, 938.

[47] J. P. Guthrie, *J. Phys. Chem. B* **2009**, *113*, 4501.

[48] J. P. Guthrie, *J. Comput.-Aided Mol. Des.* **2014**, *28*, 151.

[49] J. C. Kromann, C. Steinmann, J. H. Jensen, *J. Chem. Phys.* **2018**, *149*, 104102.

[50] S. Genheden, *J. Comput.-Aided Mol. Des.* **2017**, *31*, 867.

[51] I. Misztal, M. Perez-Enciso, *Proceedings of the World Congress on Genetics Applied to Livestock Production* **1998**, *27*, 467. http://nce.ads.uga.edu/~ignacy/numpub/oldpapers/wc98fsp.PDF

[52] C. M. Ionescu, D. Sehnal, F. L. Falginella, P. Pant, L. Pravda, T. Bouchal, R. Svobodová Vařeková, S. Geidl, J. Koča, *Aust. J. Chem.* **2015**, *7*, 50.

[53] F. Lipparini, B. Stamm, E. Cancès, Y. Maday, B. Mennucci, *J. Chem. Theory Comput.* **2013**, *9*, 3637.

[54] F. Lipparini, L. Lagardère, G. Scalmani, B. Stamm, E. Cancès, Y. Maday, J.-P. Piquemal, M. J. Frisch, B. Mennucci, *J. Chem. Phys. Lett* **2014**, *5*, 953.

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