Dependence of Vaporization Enthalpy on Molecular Surfaces and Temperature: Thermodynamically Effective Molecular Surfaces

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Approximation of molecular surfaces is of central importance in numerous scientific fields. In this study we theoretically derive a physical model to relate phase-change thermodynamics to molecular surfaces. The model allows accurately predicting vaporization enthalpy of compounds for a wide temperature range without requiring any empirical parameter. Through the new model, we conceptualize thermodynamically effective molecular surfaces and show that they, although only marginally different than van der Waals surfaces, substantially improve predictability of multiple thermodynamic quantities.

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The surface area of molecules is one of the key parameters influencing the thermodynamics of the condensed phase. Evaluation of molecular surfaces plays a key role in a large number of cutting-edge scientific fields and technologies such as drug discovery [1,2], catalysis [3], molecular biology [4–6], molecular genetics [7], and nanotechnology [8,9]. One of the chief applications of molecular surface estimation is the theoretical evaluation of solution thermodynamics via continuum solvation models [10] which is an extensively applied method in very diverse scientific fields, ranging from catalysis [11,12], advanced nanomaterials [13], surface science [14], or mechanisms of chemical reactions in the condensed phase [15,16] to unraveling the activity mechanism of coronavirus [17].

Studying the influence of molecular surfaces on condensed phase thermodynamics has been an active scientific area with a history of more than a century. One of the earliest attempts in this regard dates back to 1886 and was proposed by Eötvös. He suggested a proportionality between the free energy per unit of interfacial surface, i.e., the surface tension, and the surface area of liquid-phase molecules [18]. His work was indeed one of the earliest examples of experimental evaluation of molecular surfaces from liquid molar volume data and by assuming solution-phase molecules as perfect spheres. Although the assumption of perfect spheres is the simplest approach to get a rough estimation of molecular surfaces, it satisfactorily holds for monoatomic molecules. Accordingly, the earliest successful applications of approximating molecular surfaces to study solution thermodynamics exploit surfaces determined via perfect sphere assumption and thus, are mainly limited to noble gases [19–22].

The van der Waals (vdW) surface area concept was proposed in the pioneering work of Bondi [23], which became the cornerstone of more advanced molecular surfaces such as solvent excluded surfaces (SES) and solvent accessible surface area (SASA). Since then, numerous methods and algorithms, e.g., multiple variants of solvent excluded or solvent accessible surface areas, have been proposed to provide an estimation of molecular surfaces. The wide variety of methods and multiple parametrizations proposed for each one typically yield quite diverse estimations of molecular surfaces. For a broader comparison, we provide computed molecular surfaces for 215 molecules via different parametrizations of atomic radii based on the vdW method in Supplemental Material [37] and demonstrate their remarkable impact on predictability of multiple thermodynamic quantities in the following.

Surprisingly, despite this diversity of methods and parametrizations and quite different estimations of molecular surface they yield, there are numerous examples of reporting successful applications for each one of these methods. For example, while the GAUSSIAN03 software package used SES surfaces and UA0 atomic radii as default for polarizable continuum solvation models, for the latest release of the same software, vdW surfaces and UFF atomic radii are considered as default [24]. This is mainly because the majority of these demonstrations are based on an empirical exploitation of molecular surfaces to study solution thermodynamics [25,26]. Inaccuracies due to deviations of the employed molecular surfaces from the actual values are then corrected via *ad hoc* modifications and parametrizations, mainly applied on atomic radii. Accordingly, the most widely applied continuum solvation models exploit their specifically defined molecular surfaces and *ad hoc* modifications of atomic radii [10].

One main reason behind the diversity in defining and parametrizing molecular surfaces and requiring such *ad hoc* modification in their respective applications is that although the main application of molecular surfaces is for studying solution-phase thermodynamics, they are typically characterized using other target quantities. For example, the Bondi parametrization of atomic radii has been done using physical quantities like x-ray diffraction data, gas kinetic collision cross section, and liquid density as target quantities [23] while the UFF or UA0 atomic radii are parametrized against bond distances [27]. One main reason for that is the unavailability of a rigorous theoretical method that allows precise and analytical characterization of the relationship between molecular surfaces and solution thermodynamics without *ad hoc* modifications or parametrization.

Obviously, such a theoretical method offers several advantages. First and foremost, it allows us to characterize uniquely definable molecular surfaces with physical significance, directly through the thermodynamic data and without requiring *ad hoc* modifications. Furthermore, it allows evaluating the performance of various methods and parametrizations in reproducing those reference molecular surfaces. Additionally, it results in a better understanding and treating some of the main challenges in theoretical studies of solvation, such as the appropriate treatment of solvent effects in continuum solvation models.

To achieve this goal, in the present study we theoretically derive a relationship (see the Appendix for details) relating vaporization enthalpy (ΔH_{vap}) as a function of temperature to the molecular surfaces (a_s) stated as

$$\Delta H_{\mathrm{vap}} = \frac{a_s}{2}\left(2\gamma - T\frac{d\gamma}{dT}\right) - \frac{R}{2}T \ln\left(\frac{T}{T_c}\right), \tag{1}$$

where γ is the surface tension and T_c is the critical temperature.

Among different thermodynamic quantities of solution which can be analytically related to molecular surfaces for this purpose, the vaporization enthalpy possesses several advantages. The main one is that vaporization enthalpy can be directly determined experimentally, while free energy or entropy can only be determined indirectly and via measuring the temperature dependence of vaporization enthalpy or equilibrium vapor pressures at multiple temperatures. It implies the accumulation of errors inherent in both experimental measurements and the subsequent computations. The more convenient experimental procedure for enthalpy measurement has also made accurate benchmark datasets for them more readily available, which is another advantage of using vaporization enthalpy. Finally, evaluation of molecular surfaces via vaporization enthalpy is not only both more accurate and less challenging but also once it is found, it can be conveniently used to obtain other thermodynamic quantities, via the fundamental thermodynamic relationships, as shown in the following.

By studying relationships proposed in the past century to analytically relate solution thermodynamics to molecular surfaces, we found two models that although proposed empirically, show obvious similarities to our theoretically derived model. In the first model, the free energy of solvation ($\Delta G_{\mathrm{solvation}}$) is related to the solvent excluded surface of molecules $\mathcal{A}$ and surface tension via [19–22,26,28,29]:

$$\Delta G_{\mathrm{solvation}} = \mathcal{A}\gamma + \mathcal{B}, \tag{2}$$

where $\mathcal{B}$ is a constant [30]. On the other hand, in the second model, a very similar relationship commonly known as Kabo's relationship is proposed for relating vaporization enthalpy, surface tension, and molecular surfaces via [31]

$$\Delta H_{\mathrm{vap}} = \mathcal{A}(V^{2/3}\gamma) + \mathcal{B}. \tag{3}$$

In Kabo's relationship, V is the liquid molar volume and $\mathcal{A}$ and $\mathcal{B}$ are constants. Noteworthy, the right-hand side of Kabo's relationship closely matches the right-hand side of Eq. (2) with the only difference that in Kabo's relationship, the prefactor of the surface tension is in fact molecular surfaces evaluated based on the perfect sphere assumption as discussed earlier, while in Eq. (2) this factor is a solvent excluded surface of molecules [30].

Despite a general similarity in functional form for the two abovementioned models and our proposed one, clear inconsistencies among them necessitates a careful and rigorous verification of the newly proposed model.

To that end, we first evaluated the accuracy of vaporization enthalpies predicted via the newly developed relationship and compared it with the Kabo's method as the other model available for the same purpose. Accordingly, for a dataset of 215 molecules, we computed the value of the a_s parameter required by Eq. (1) which yielded the lowest error in predicting vaporization enthalpies over a wide temperature range from melting point to critical point for each compound (further details on the studied dataset are provided in Supplemental Material [32]). Via optimized values of a_s which are in fact our proposed "thermodynamically effective" molecular surfaces, an average absolute deviation (AAD) of 0.188 kcal/mol was obtained for the predicted vaporization enthalpies. This resulting AAD is within both the chemical accuracy and the reported accuracy of the reference experimentally determined data.

While the newly derived relationship with only one fitted parameter yielded an AAD of 0.188 kcal/mol, the Kabo's method with two fitted parameters optimized for each compound, could not yield an AAD better than 0.402 kcal/mol. The same comparison between our proposed relationship and Eq. (2) as the other conventionally accepted empirical model for relating solution thermodynamics to molecular surfaces provided in the following also reveals a much higher accuracy for our proposed model.

To evaluate the significance of the $T(d\gamma/dT)$ and $-(R/2)T\ln(T/T_c)$ terms, which are the most obvious differences between our proposed relationship and the two empirically proposed models, we reoptimized a_s parameters for the two following relationships:

$$\Delta H_{\mathrm{vap}} = a_s\gamma - \frac{R}{2}T\ln\left(\frac{T}{T_c}\right), \tag{4}$$

and

$$\Delta H_{\mathrm{vap}} = \frac{a_s}{2}\left(2\gamma - T\frac{d\gamma}{dT}\right), \tag{5}$$

which are two variants of Eq. (1) obtained by removing the term being studied. Using the reoptimized a_s parameters, the two abovementioned variants yielded higher AADs with values of 2.071 and 0.197 kcal/mol, respectively. These results clearly show the veracity of the proposed model and confirm that both terms ($T(d\gamma/dT)$ and $-(R/2)T\ln(T/T_c)$) play a significant role in improving predictability of solution thermodynamics through molecular surfaces. Among them, the $T(d\gamma/dT)$ term has the more significant impact and its overlooking reduces the accuracy of predicted vaporization enthalpies by one order of magnitude.

Up to this point, we have introduced a (theoretically derived) relationship and have demonstrated that it can accurately predict vaporization enthalpy of various compounds for wide temperature ranges. We argued that the only adjustable parameter in this equation, a_s, is interpreted as an estimation of molecular surfaces. Considering that the newly conceptualized molecular surface, unlike conventionally defined ones, is determined through thermodynamic data, we call it as thermodynamically effective surface of a molecule.

The quite different approach of determining molecular surfaces via phase-change thermodynamic data, entices us to investigate how the thermodynamically effective surfaces compare with the conventionally accepted molecular surfaces. To that end, we first studied the accuracy of vaporization enthalpies predicted using our proposed model for the case the parameter a_s, instead of being determined as a fitted parameter, were vdW molecular surfaces computed via well-stablished computer algorithms (see Supplemental Material [32] for details of computations).

According to the results, vdW surfaces computed based on Bondi, UFF, UA0, and Pauling parametrizations of atomic radii yielded AADs of 0.623, 1.078, 1.256, and 0.867 kcal/mol for vaporization enthalpies predicted via Eq. (1), respectively. These results reveal the possibility of predicting vaporization enthalpy from melting point to critical temperature with AAD as low as 0.623 kcal/mol through the new model without requiring any empirical parameter which is not achievable by other available models, to the best of our knowledge. Additionally, these results clearly show that slight differences in approximating molecular surfaces due to different parametrizations of atomic radii can have a remarkable impact on the predictability of thermodynamic quantities.

Very interestingly, by comparing the vdW surfaces computed based on the Bondi parametrization of atomic radii which yielded the most accurate results as demonstrated above and thermodynamically effective surfaces computed via phase-change thermodynamic data, we observed a deviation of only 5% and a high correlation coefficient ($R = 0.957$) between them as depicted in Fig. 1.

In addition to the above-mentioned vdW surfaces, for each molecule, we also studied 252 variants of vdW and SASA molecular surfaces which differ in parametrization and scaling of atomic radii (see Supplemental Material [32] for further details). According to the results, while via the solvent accessible surfaces we could not achieve any AAD better than 7.889 kcal/mol, for the vdW surfaces the best results with AAD of 0.568 kcal/mol were obtained for UA0 atomic radii scaled by 0.9. For a better illustration, the AADs of predicted vaporization enthalpies obtained via Eq. (1) for different scaling and parametrizations of atomic radii are compared in Fig. 2.

In addition to vdW surfaces, we also studied molecular surfaces computed from molar volumes and based on the perfect sphere assumption. Using the molecular surfaces evaluated from molar volumes at the melting point and without any adjustable parameters, Eq. (1) yielded an AAD of 0.561 kcal/mol for the whole dataset and the whole temperature range. On the other hand, using molecular surfaces obtained via molar volumes at normal boiling points resulted in AAD of 1.248 kcal/mol. These results show why the perfect sphere assumption is not generally a

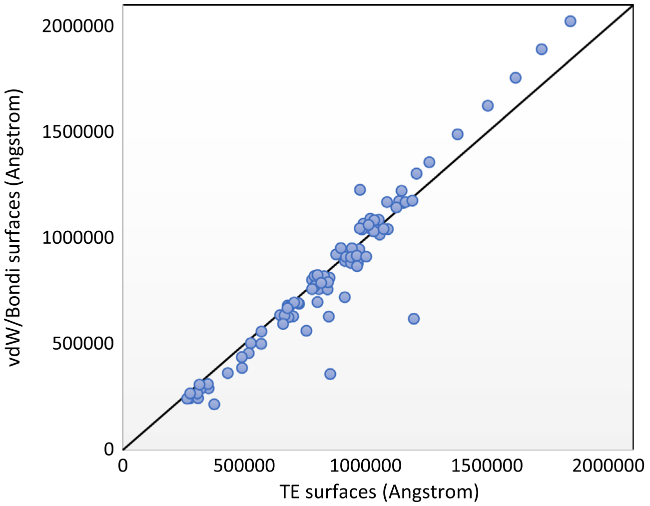

FIG. 1. Comparison of thermodynamically effective (TE) surfaces and vdW surfaces computed based on Bondi parametrization.

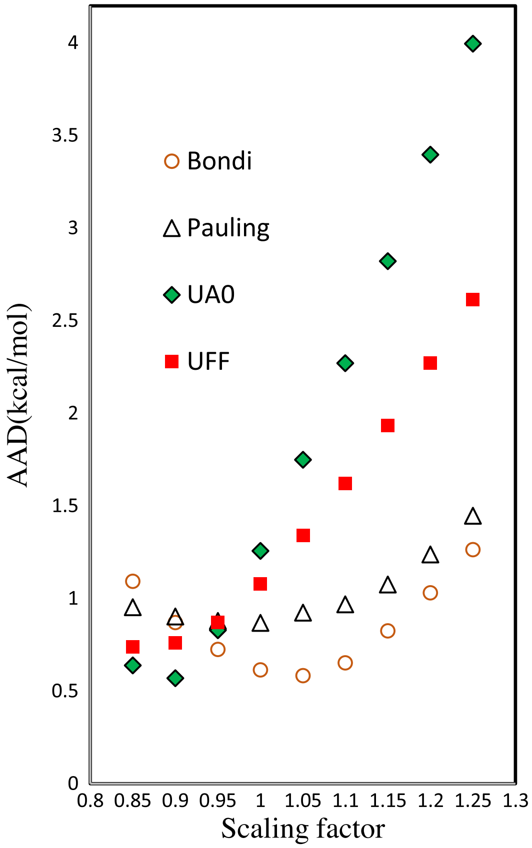

FIG. 2. Comparison of AAD of vaporization enthalpies predicted by Eq. (1) using vdW surfaces based on various parametrizations of atomic radii.

rigorous approach for evaluating molecular surfaces. In addition to lower accuracy in describing temperature dependence of vaporization enthalpy compared to the thermodynamically effective molecular surfaces, it totally overlooks temperature dependence of molar volume and its impact on the evaluated molecular surfaces.

In Fig. 3, the temperature dependence of vaporization enthalpy of some of the most widely used solvents predicted via Eq. (1) using various estimations of molecular surfaces are compared. These results reveal the significant importance of evaluated molecular surfaces on the accuracy of obtained results on the one hand, and the robustness and reliability of the newly derived relationship and the thermodynamically effective molecular surfaces on the other hand.

As it was discussed earlier, one of the main advantages of characterizing the dependency of solution thermodynamics on molecular surfaces through temperature dependence of vaporization enthalpy is its straightforward transferability to other thermodynamic quantities.

As one of the most important thermodynamic quantities, evaluation of the solvation free energy can be achieved via the Gibbs-Helmholtz relationship, resulting in an AAD of only 0.057 kcal/mol for our studied dataset

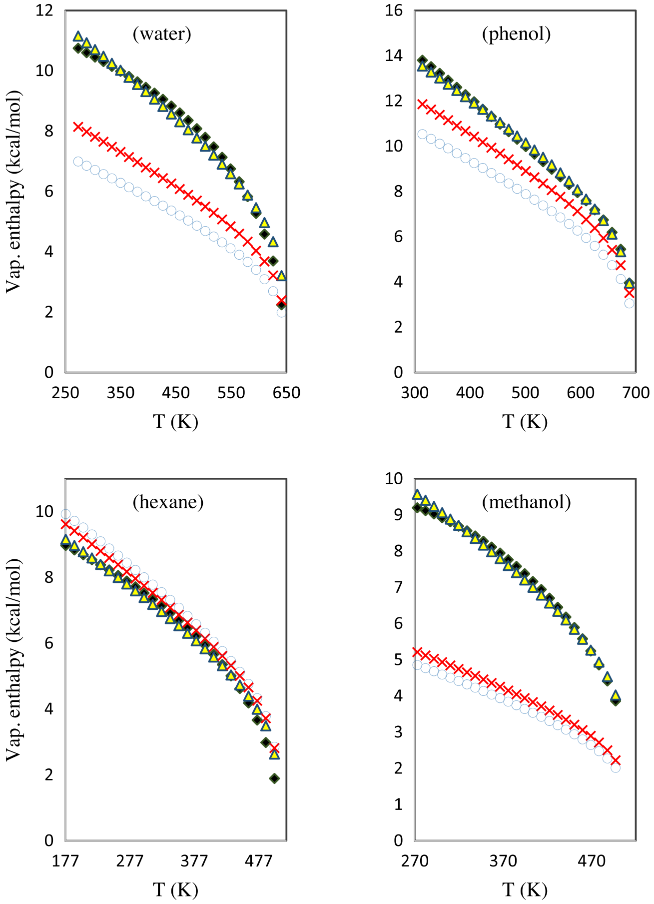

FIG. 3. Comparison of experimentally determined vaporization enthalpy at various temperatures (green diamonds) and predicted data via the newly proposed model based on the following: thermodynamically effective surfaces (yellow triangles), perfect sphere surfaces computed via molar volumes at melting point (red crosses), and vdW surfaces (blue spheres).

(see Supplemental Material [32] for details). On the other hand, the computation of solvation free energy via Eq. (2) as one of the two empirically proposed models, results in an AAD of 1.166 kcal/mol which is much less accurate than the results we obtained based on the new method. These results also suggest that considering linear proportionality between vaporization enthalpy and surface tension, which has already been empirically suggested in Kabo's relationship and is supported by our theoretical approach, is more valid than the other conventionally employed relationships which consider the same proportionality between solvation free energy and surface tension.

We also studied predictability of experimentally determined standard state solvation free energies reported in the Minnesota solvation database [37] via our physical model and thermodynamically effective surfaces for the solutions common between the DIPPR and Minnesota solvation databases. For the new model we could obtain an AAD of only 0.1215 kcal/mol which is by almost a factor of 2 more accurate than best results reported for advanced continuum solvation models [10] obtained through a very laborious procedure [38]. Details of computed solvation free energies for individual compounds are reported in Supplemental Material [32].

In addition to the solvation free energy, the saturation vapor pressure (P^{sat}) as another extensively required thermodynamic quantity in many industrial and scientific applications can also be accurately computed via the thermodynamically effective surfaces via the Clausius–Clapeyron relation (the details of computations are provided in Supplemental Material [32]). A comparison of predicted and experimentally determined saturation vapor pressures for some of most widely used solvents is depicted in Fig. 4. The excellent agreement between the theoretically evaluated and experimental data depicted in Fig. 4 implies the robustness of our proposed thermodynamically effective surfaces.

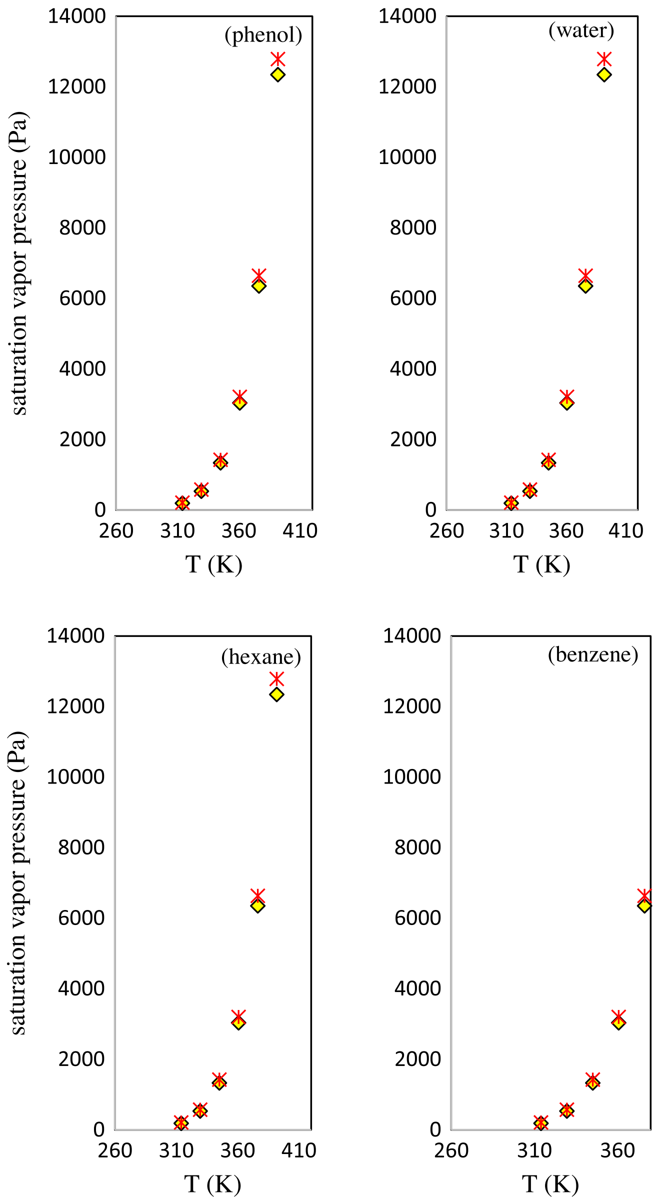

FIG. 4. Comparison of theoretically predicted saturation vapor pressures obtained via Eq. (1) and thermodynamically effective surfaces (red) and experimentally determined data (yellow).

It should be noted that in the present study, we employed ideal gas low in deriving Eq. (1). For the main purpose of this Letter which has been an estimation of molecular surfaces and prediction of vaporization enthalpy at atmospheric temperature where nonideality impacts are negligible [39], this will not remarkably influence the accuracy of the results. Nevertheless, for evaluation of thermodynamic quantities at higher pressures, where nonideality becomes important, one might need to consider employing more accurate equations of state.

In summary, in the context of the present study, we theoretically proposed a physical model to describe the dependency between solution thermodynamics and molecular surfaces and demonstrated that the new model outperformed the two other models empirically proposed for the same purpose within the last century. Using vdW molecular surfaces with Bondi parametrization of atomic radii, the proposed physical model allowed predicting vaporization enthalpy of diverse compounds from melting point to critical temperature with AAD of 0.623 kcal/mol, without requiring any empirical parameter which is not possible by other available models.

Through the proposed physical model, we conceptualized thermodynamically effective surfaces. We demonstrated that the thermodynamically effective surfaces, although estimated quite differently and using phase-change thermodynamic data, were only slightly different than empirically proposed vdW surfaces. However, this slight deviation yielded a substantial improvement in the predictability of multiple thermodynamic quantities. Consequently, we propose the thermodynamically effective surfaces as a reliable alternative for the currently defined methods for characterizing molecular surfaces, especially for studying the condensed phase thermodynamics.

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Appendix: Derivation of the proposed physical model.—By considering vaporization as a dynamic process at which evaporation and condensation have the same rates and equating the rates of evaporation and condensation described by transition state theory and some manipulations, the ratio of partition functions of the gas and liquid phases is obtained as [40]

$$\frac{Q^g}{Q^s} = \frac{N_a P^{\mathrm{sat}}}{P}\left(\frac{k_B T}{2\pi m}\right)^{1/2}\frac{h}{k_B T[n_s]}\exp\left(\frac{\Delta\varepsilon_{sg}}{k_B T}\right), \qquad \text{(A1)}$$

where N_a is Avogadro's constant, P^{sat} is the saturation vapor pressure of the liquid, $\Delta\varepsilon_{sg}$ is the energy for moving one molecule from the liquid surface to the gas phase, and k_B and h are Boltzmann and Planck constants, respectively. Using the statistical thermodynamics relationship between the energy and partition function stated as

$$\langle\varepsilon\rangle = k_B T^2 \frac{\partial \ln(Q)}{\partial T}, \tag{A2}$$

and with some algebraic manipulations, it can be shown that the temperature dependence of the vaporization enthalpy follows [40]

$$\Delta h_{\mathrm{vap}} = \Delta\varepsilon_{bs} - \frac{k_B}{2} T \ln(T) - T \int \frac{\Delta\varepsilon_{bs}}{T^2} dT + CT, \tag{A3}$$

where C is a constant and $\Delta\varepsilon_{bs}$ is the energy required for moving one molecule from the bulk of the liquid to the surface. Evaluation of $\Delta\varepsilon_{bs}$ via experimentally measurable quantities can be achieved using the fundamental thermodynamics relationships between energy (ε), Helmholtz free energy (f), and entropy (s), which implies [40]:

$$\Delta\varepsilon_{bs} = \Delta f_{bs} - T \frac{d(\Delta f_{bs})}{dT}, \tag{A4}$$

where Δf_{bs} is the free energy change for moving one molecule from the bulk of liquid to the surface. Another straightforward way to obtain Eq. (A4) is using the Gibbs-Helmholtz equation:

$$\frac{d(\frac{f}{T})}{dT} = -\frac{\varepsilon}{T^2}, \tag{A5}$$

which implies

$$\frac{1}{T}\frac{df}{dT} - \frac{f}{T^2} = -\frac{\varepsilon}{T^2}, \tag{A6}$$

This then clearly yields Eq. (A4) by subtracting the resulting equations for the bulk and surface states.

Exploiting the thermodynamics relationship among Δf_{bs}, surface tension (γ), and the molecular surface area (a_s) which is defined as [40]

$$\Delta f_{bs} = \frac{a_s}{2}\gamma, \tag{A7}$$

Eq. (4) can be rewritten as

$$\Delta\varepsilon_{bs} = \frac{a_s}{2}\left(\gamma - T\frac{d\gamma}{dT}\right). \tag{A8}$$

Halving the molecular surfaces a_s in Eq. (A7) is considered here because in fact only one half of the molecular surfaces contribute in forming the gas-liquid interface and the other half remains in the bulk of the liquid [40,41].

By substituting Eq. (A8) into Eq. (A3) and using $[d(\gamma/T)/dT] = \{[T(d\gamma/dT) - \gamma]/T^2\}$ and multiplying both sides by Avogadro's number, the correlation between the surface tension and molar vaporization enthalpy (ΔH_{vap}) is obtained as

$$\Delta H_{\mathrm{vap}} = \frac{a_s}{2} N_A \left(2\gamma - T\frac{d\gamma}{dT}\right) - \frac{R}{2} T \ln(T) + \beta T, \tag{A9}$$

in which β is a constant. Knowing that at the critical temperature both vaporization enthalpy and surface tension approach zero, and due to the continuity of the surface tension, the $(d\gamma/dT)$ term also approaches zero, the constant β is found as

$$\beta = \frac{R}{2}\ln(T_c), \tag{A10}$$

which by substitution into Eq. (A9) finally yields Eq. (1).

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