FREE ENERGY OF A SOLVENT MOLECULE: CONVENTIONAL IDEAL GAS APPROXIMATION *VS.* EXPERIMENTAL THERMODYNAMIC DATA

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Solvents modify reaction thermodynamics and kinetics through specific coordination, demanding the correct treatment of the role of the medium in molecular modeling. Computationally cheap implicit solvation models are commonly used to capture bulk electrostatic effects; however, the additional incorporation of solvent molecules into computational models is often essential for obtaining reliable results. The latter technique is specifically justified for processes in which solvent molecules are released into the bulk or become bound, behaving as active participants, such as in intermediates or transition states with high polarity differences. In this study, we compare Sackur-Tetrode (ST)-based conventional models, which treat the solute and solvent on equal terms, with Gibbs free energies derived from experimental thermochemical data for various solvents and assess the performance of the latter on a series of solvent–ligand exchange reactions.

Empirical free energy values for solvents were derived *via* a Hess cycle comprising experimental liquid-phase enthalpy, entropy (from low-temperature adiabatic vacuum calorimetry), and zero-point energy (from IR/Raman spectroscopy). Conventional ideal gas values were calculated using the DFT method at the PBE0/def2-TZVP level of theory, with symmetric and asymmetric reference states represented with 1 M and solvent self-concentration in the ST equation, respectively. While conventional approaches usually provide free energy contributions lying within 1 kcal·mol^{-1} from the experimental ones, in some cases they deviate by ∼2 kcal·mol^{-1}; meanwhile, combining free volume correction with an asymmetric reference state yielded the best MAE in entropy values (1 kcal·mol^{-1}).

To validate the accuracy of experimental solvent Gibbs free energies, a dataset comprising complexation reactions with thermochemical data obtained via isothermal titration calorimetry (ITC) was compiled. For solvents where experimental and calculated values differ by >2 kcal·mol^{-1}, the experimental free energy contributions provide 1−2 kcal·mol^{-1} more accurate results for solvent−ligand exchange reactions, demonstrating that experimentally derived energy components can be combined with computed ones to yield improved results. None of the conventional approximations is universal, as they exhibit divergent trends for different solvents.

To conclude, Gibbs free energies for solvent molecules provide a compelling alternative to those calculated with ideal gas approximations, resulting in better agreement with experimental thermodynamic parameters.

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