# Supporting Information

# "Hydration of Aromatic Heterocycles as Adversary of π-Stacking"

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Table S1: Descriptors and experimental data for all heteroaromatics.

| Name | Dipole Debye* | Sum of "Heterocharges"** | Interaction (kcal/mol) | Experiment (kcal/mol)[1] |
|---|---|---|---|---|
| Benzene | 0.00 | 0.00 | -3.56 | -0.86 |
| Pyridine | 2.10 | -0.68 | -4.07 | -4.69 |
| Pyridazine | 4.01 | -0.90 | -4.93 | |
| Pyrazine | 0.00 | -0.66 | -4.49 | |
| Pyrimidine | 2.20 | -1.68 | -4.72 | |
| Furan | 0.50 | -0.17 | -3.34 | -3.47 |
| Oxazole | 1.52 | -0.80 | -3.80 | |
| Isoxazole | 2.84 | -0.55 | -4.05 | |
| Thiophene | 0.56 | 0.02 | -3.52 | -1.60 |
| Thiazole | 1.42 | -0.49 | -3.86 | |
| Pyrrole | 2.02 | -0.50 | | -4.78 |
| Imidazole | 3.73 | -1.06 | | |
| Pyrazole | 2.25 | -0.81 | | |
| Naphthalene | 0.00 | 0.00 | -5.60 | -2.40 |
| Quinoline | 2.18 | -0.72 | -5.72 | -5.72 |
| Isoquinoline | 2.42 | -0.65 | -5.97 | |
| Cinnoline | 4.05 | -0.68 | -6.05 | |
| Phtalazine | 4.96 | -0.69 | -6.31 | |
| Quinazoline | 2.78 | -1.68 | -6.21 | |
| Quinoxaline | 0.39 | -1.06 | -5.66 | |
| Pteridine | 2.52 | -2.64 | -6.77 | |
| Pyridazino[4,5-d]pyridazine | 0.00 | -1.18 | -7.85 | |
| Pyrimidino[4,5-d]pyrimdine | 2.54 | -3.42 | -7.70 | |
| Pyrazino[2,3-b]pyrazine | 0.00 | -2.14 | -6.39 | |
| Benzothiophene | 0.68 | -0.08 | -5.26 | |
| Benzothiazole | 1.18 | -0.72 | -5.17 | |
| Benzofurane | 0.69 | -0.30 | -5.08 | |
| Benzoxazole | 1.26 | -1.06 | -5.51 | |
| Indole | 2.24 | -0.08 | -5.56 | |
| Benzimidazole | 3.49 | -0.89 | -6.44 | |
| Indazole | 1.66 | 0.34 | -5.68 | |
| 1,7-Diazaindene | 3.89 | -0.91 | -5.24 | |
| Benzotriazole | 1.60 | -0.36 | -6.10 | |
| Purine | 3.66 | -2.48 | -6.54 | |
| Indolizine | 1.27 | -0.28 | -5.73 | |
| Pyrrolo[1,2-a] pyridazine | 3.38 | -0.59 | -6.28 | |
| Pyrrolo[1,2-b] pyridazine | 1.58 | 0.01 | -4.02 | |
| 2-Azaindene | 3.05 | -0.19 | -6.21 | |
| Thienothiophene | 1.23 | 0.07 | -5.03 | |
| Imidazothiazole | 3.91 | -0.15 | -5.71 | |

*Molecular dipole moments were calculated using Gaussian09[2]; **The charges of the heteroatoms were obtained using RESP[3].

Table S2: Correaltions of our GIST approach with the solvation free energies published in the FreeSolv4 database

| Pearson Correlation | GIST | FreeSolv | Experiment |
|---|---|---|---|
| GIST | **1.00** | **0.93** | **0.96** |
| FreeSolv | **0.93** | **1.00** | **0.96** |
| Experiment | **0.96** | **0.96** | **1.00** |

Table S3: Pearson correlations of entropy values calculated from GIST, TI at different temperatures (Temp) and long simulations of the endpoints of the alchemical transformations (EP).

| **T$\Delta$S** | **GIST** | **Temp** | **EP** |
|---|---|---|---|
| GIST | 1.00 | 0.59 | 0.60 |
| TEMP | 0.59 | 1.00 | 0.63 |
| EP | 0.60 | 0.63 | 1.00 |

Table S4: Interaction energies for a single water molecule with benzene at optimized distances. Calculations were performed using DFT at $\omega$B97XD with the cc-pVTZ basis set[5]. All coordinates were restrained except for the hydrogen atoms of the water molecule.

| **Position** | **Distance** | **Energy** |
|---|---|---|
| **Center** | 3.3 Å | -4.6 kcal/mol |
| **Atom** | 3.1 Å | -3.7 kcal/mol |
| **Bond** | 3.1 Å | -3.6 kcal/mol |

Table S5: RMSE calculated for the thermodynamic properties calculated using GIST and TI and the experimental $\Delta$G values.

| **Set 1** | **Set 2** | **RMSE** |
|---|---|---|
| **$\Delta G_{GIST}$** | $\Delta G_{TI}$ | 1.29 |
| **$\Delta H_{GIST}$** | $\Delta H_{TI}$ | 2.87 |

| | | |
|---|---|---|
| $\Delta S_{GIST}$ | $\Delta S_{TI}$ | 2.63 |
| $\Delta G_{GIST}$ | $\Delta G_{Experiment}$ | 1.09 |
| $\Delta G_{TI}$ | $\Delta G_{Experiment}$ | 1.23 |

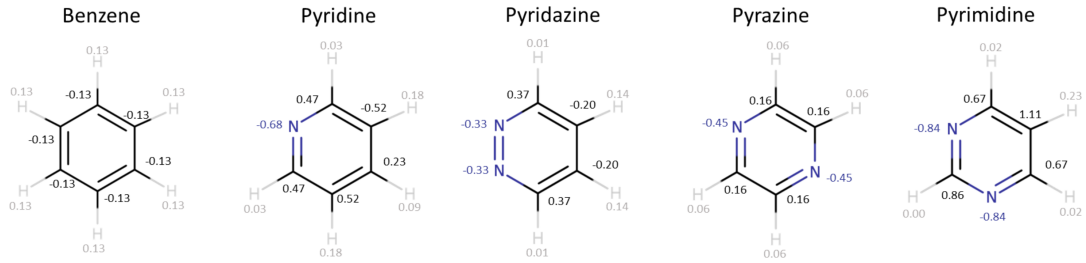


Figure S1. Charges used in the GIST and TI simulations obtained from FF parametrization using HF/6-31G* and a RESP fit implemented in AmberTools for group 1 molecules.

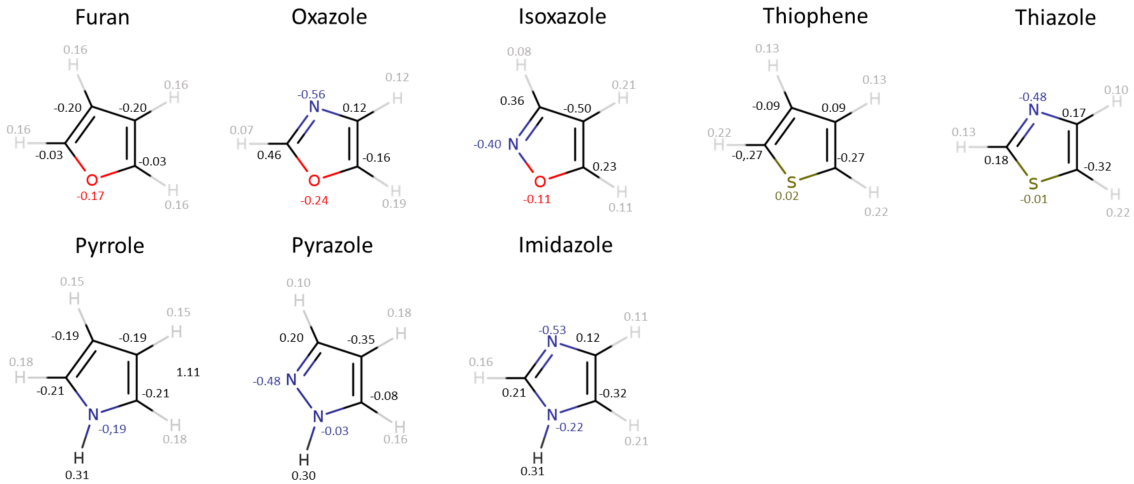


Figure S2: Charges used in the GIST and TI simulations obtained with HF/6-31G* and a RESP fit implemented in antechamber for group 2.

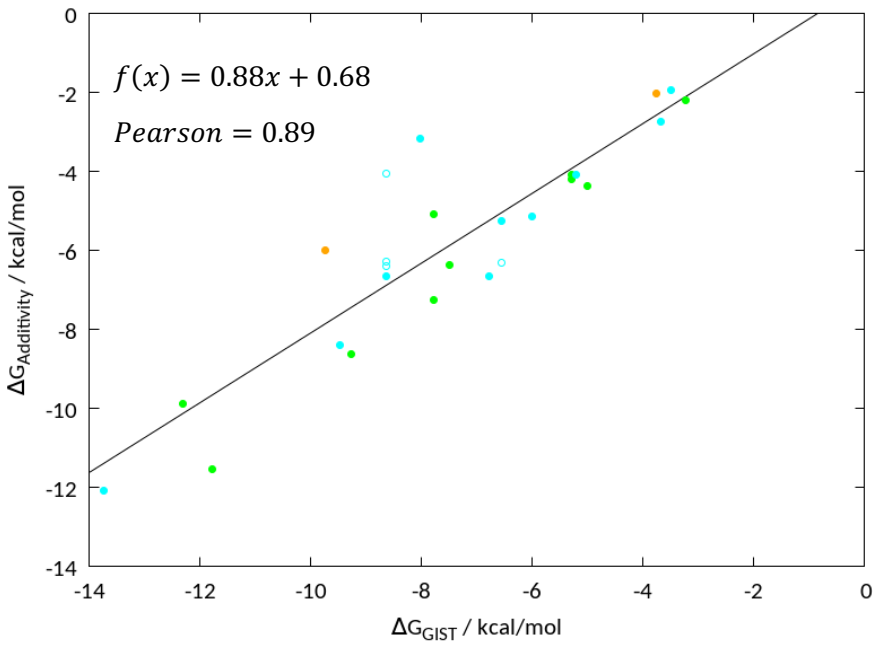


Figure S3: Correlation of solvation free energy calculated for bicycles calculated directly using GIST and calculated from the solvation free energy of the respective monocycles. The green circles represent two fused 6-membered rings, the full cyan circles fused 5-6 membered rings where no nitrogen tom is in position 8 or 9, the hollow cyan circles show fused 5-6 membered rings with a nitrogen in position 8 and the orange circles represent fused 5-5 membered rings.

Table S6: Combinations of monocycles used to calculate the respective bicyclic aromatics.

| Monocycle 1 | $\Delta G_{Solv}$ kcal/mol | Monocycle 2 | $\Delta G_{Solv}$ Kcal/mol | Bicycle | $\Delta G_{Solv}$ kcal/mol | Reference kcal/mol |
|---|---|---|---|---|---|---|
| Benzene | -1,61 | Benzene | -1,61 | Naphthalene | -3,22 | -2,21 |
| Benzene | -1,61 | Pyridine | -3,68 | Quinoline | -5,29 | -4,09 |
| Benzene | -1,61 | Pyridine | -3,68 | Isoquinoline | -5,29 | -4,20 |
| Benzene | -1,61 | Pyridazine | -6,16 | Cinnoline | -7,77 | -5,08 |
| Benzene | -1,61 | Pyridazine | -6,16 | Phtalazine | -7,77 | -7,27 |
| Benzene | -1,61 | Pyrimidine | -5,89 | Quinazoline | -7,50 | -6,37 |
| Benzene | -1,61 | Pyrazine | -3,43 | Quinoxaline | -5,04 | -4,38 |
| Pyrazine | -3,43 | Pyrimidine | -5,89 | Pteridine | -9,32 | -8,62 |
| Pyridazin | -6,16 | Pyridazine | -6,16 | Pyridazino[4 5d]pyridazine | -12,32 | -9,87 |
| Pyrimidine | -5,89 | Pyrimidine | -5,89 | Pyrimidino[4 5d]pyrimdine | -11,78 | -11,54 |
| Pyrazine | -3,43 | Pyrazine | -3,43 | Pyrazino[2 3b]pyrazine | -6,86 | -6,65 |
| Benzene | -1,61 | Thiophene | -1,88 | Benzothiophene | -3,49 | -1,95 |
| Benzene | -1,61 | Thiazole | -3,60 | Benzothiazole | -5,21 | -4,09 |
| Benzene | -1,61 | Furane | -2,07 | Benzofurane | -3,68 | -2,73 |
| Benzene | -1,61 | Oxazole | -4,39 | Benzoxazole | -6,00 | -5,15 |
| Benzene | -1,61 | Pyrrole | -4,95 | Indole | -6,56 | -5,25 |
| Benzene | -1,61 | Imidazole | -7,86 | Benzimidazole | -9,47 | -8,41 |
| Benzene | -1,61 | Pyrazole | -6,41 | Indazole | -8,02 | -3,18 |
| Pyridine | -3,68 | Pyrrole | -4,95 | 1,7-Diazaindene | -8,63 | -6,66 |
| Pyrimidine | -5,89 | Imidazole | -7,86 | Purine | -13,75 | -12,09 |
| Benzene | -1,61 | Pyrrole | -4,95 | Indolizine | -6,56 | -6,32 |
| Pyridine | -3,68 | Pyrrole | -4,95 | Pyrrolo[1 2a] pyrimidine | -8,63 | -6,29 |
| Pyridine | -3,68 | Pyrrole | -4,95 | Pyrrolo[1 2b] pyridazine | -8,63 | -4,07 |
| Pyridine | -3,68 | Pyrrole | -4,95 | 2-Azaindolizine | -8,63 | -6,39 |
| Thiophene | -1,88 | Thiophene | -1,88 | Thienothiophene | -3,76 | -2,04 |
| Imidazole | -7,86 | Thiophene | -1,88 | Imidazothiazole | -9,74 | -5,99 |

## NVT Calculations

Table S7: Solvation free energies calculated using GIST in NpT ensemble, TI and GIST in NVT ensemble.

| **Compound** | **ΔG(GIST) NpT** | **ΔG TI** | **ΔG(GIST) NVT** |
|---|---|---|---|

| | / kcal/mol | / kcal/mol | / kcal/mol |
|---|---|---|---|
| **Benzene** | -1.61 | -0.95 | -1.55 |
| **Pyridine** | -3.68 | -3.20 | -3.18 |
| **Pyridazine** | -6.16 | -6.17 | -5.18 |
| **Pyrazine** | -3.82 | -3.43 | -3.82 |
| **Pyrimidine** | -5.89 | -6.49 | -4.79 |

For the GIST calculations in the different ensembles we found a Pearson correlation of 0.98, for the GIST calculations in NVT and the TI calculations 0.97.

## Water-benzene interaction

To characterize the interaction energy of water with benzene and to allow better comparability with previously published results, we calculated the interaction energy of a single water molecule with benzene at different heights from 2.3 to 4.1 Å with a step-size of 0.2 Å. These calculations were performed at three different positions for the water's oxygen atom. All coordinated were restrained except for the hydrogen atoms of the water molecule. We used DFT-wB97XD6 with the cc-pVDZ5 basis.

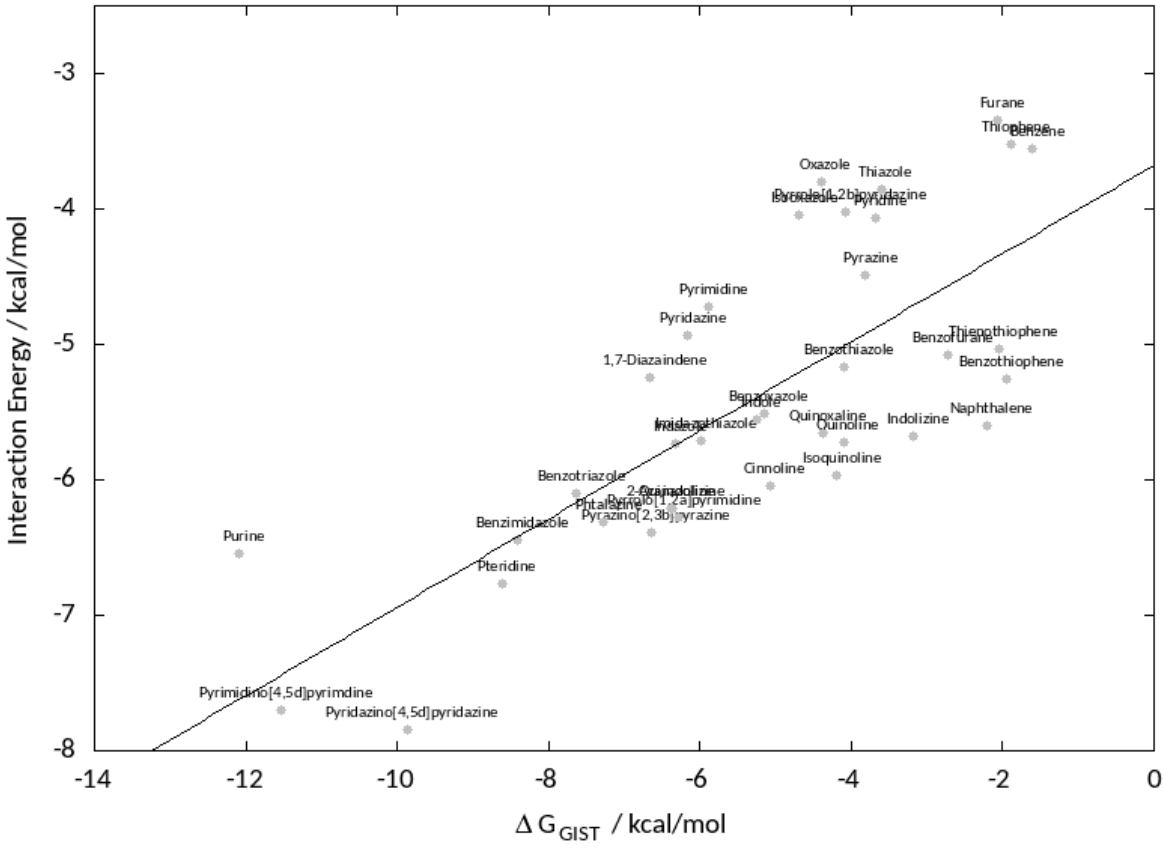


Figure S4: Interaction energy correlating with solvation free energy calculated with GIST including the compound names.


(1) Mobley, D. L.; Bayly, C. I.; Cooper, M. D.; Shirts, M. R.; Dill, K. A. Small Molecule Hydration Free Energies in Explicit Solvent: An Extensive Test of Fixed-Charge Atomistic Simulations. *Journal of Chemical Theory and Computation* **2009**, *5* (2), 350–358. https://doi.org/10.1021/ct800409d.

(2) M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox. *Gaussian 09*; Gaussian Inc. Wallingford CT, 2009.

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(4) Mobley, D. L.; Guthrie, J. P. FreeSolv: A Database of Experimental and Calculated Hydration Free Energies, with Input Files. *J Comput Aided Mol Des* **2014**, 711–720. https://doi.org/10.1007/s10822-014-9747-x.

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(6) Chai, J.-D. Long-Range Corrected Hybrid Density Functionals with Damped Atom-Atom Dispersion Corrections. *Lawrence Berkeley National Laboratory* **2009**.