Supporting Information

Enthalpic and Entropic Contributions to Hydrophobicity

Michael Schauperl†, Maren Podewitz†, Birgit J. Waldner† and Klaus R. Liedl†∗

† Institute of General, Inorganic and Theoretical Chemistry, and Center for Molecular Biosciences Innsbruck (CMBI), University of Innsbruck, Innrain 80-82, A-6020 Innsbruck, Tyrol, Austria

∗klaus.liedl@uibk.ac.at

Further decomposition of calculated thermodynamic properties

As outlined in the methodology section total solvation free energies, enthalpies, and entropies, these thermodynamic values are further decomposed. According to Eq. (3), the total enthalpy \( \Delta H_{\text{solv}} \) can be split into the enthalpic interactions between the solute and the water \( \Delta H_{\text{sw}} \) and an enthalpy term describing the distortion of the water-water interactions \( \Delta H_{\text{ww}} \). The total entropy \( \Delta S_{\text{solv}} \) is split into an orientational \( \Delta S_{\text{orient}} \) and a translational term \( \Delta S_{\text{trans}} \) (compare Eq. (4)). The origin of these terms is explained in the methods section of the main text.
Table S1: Decomposition of the thermodynamic properties for the TIP3P water model.

| Amino Acid | $\Delta H_{W}$ | $\Delta H_{WW}$ | $\Delta H_{Solv}$ | $-T\Delta S_{orient}$ | $-T\Delta S_{trans}$ | $-T\Delta S_{Solv}$ | $\Delta G_{Solv}$ |
|------------|----------------|----------------|----------------|-----------------------|---------------------|-------------------|-----------------|
| ALA        | -43.2±1.8      | 20.6±1.0       | -22.5±0.8       | 9.5±0.0               | 5.3±0.1             | 14.8±0.1          | -7.7±0.7        |
| ARG(+)     | -121.9±4.2     | 57.2±2.1       | -64.7±2.1       | 14.7±0.3              | 9.3±0.2             | 24.1±0.5          | -40.7±1.6       |
| ASN        | -63.5±7.0      | 29.7±3.0       | -33.8±4.0       | 12.2±0.6              | 6.9±0.3             | 19.1±0.9          | -14.7±3.2       |
| ASP(-)     | -141.8±0.7     | 61.2±0.4       | -80.5±0.3       | 18.2±0.1              | 8.2±0.1             | 26.4±0.0          | -54.2±0.3       |
| CYS        | -46.8±3.5      | 22.9±1.5       | -23.9±2.0       | 9.6±0.2               | 5.7±0.2             | 15.3±0.4          | -8.5±1.7        |
| GLN        | -68.1±2.5      | 32.3±1.4       | -35.8±1.1       | 13.2±0.2              | 7.4±0.2             | 20.6±0.4          | -15.2±0.7       |
| GLU(-)     | -137.6±3.4     | 59.3±1.5       | -78.3±1.9       | 19.0±0.0              | 8.7±0.2             | 27.7±0.2          | -50.6±1.7       |
| GLY        | -42.9±1.1      | 20.5±0.7       | -22.4±0.4       | 8.9±0.0               | 5.2±0.0             | 14.0±0.1          | -8.4±0.4        |
| HIS        | -67.6±1.2      | 31.6±0.3       | -36.0±1.0       | 13.5±0.2              | 7.6±0.0             | 21.1±0.2          | -14.9±0.8       |
| HIS(+)     | -108.5±3.9     | 50.9±2.3       | -57.7±1.6       | 13.2±0.3              | 8.3±0.1             | 21.5±0.3          | -36.2±1.3       |
| ILE        | -49.7±0.5      | 24.2±0.2       | -25.4±0.5       | 11.3±0.0              | 6.8±0.1             | 18.1±0.1          | -7.3±0.6        |
| LEU        | -49.0±1.2      | 24.1±0.5       | -24.9±0.7       | 11.2±0.2              | 6.6±0.1             | 17.8±0.3          | -7.1±0.5        |
| LYS(+)     | -126.6±4.5     | 60.5±2.0       | -66.1±2.5       | 14.3±0.3              | 8.5±0.5             | 22.8±0.7          | -43.4±1.9       |
| MET        | -54.1±0.6      | 26.5±0.5       | -27.6±0.6       | 11.4±0.1              | 6.7±0.0             | 18.1±0.1          | -9.5±0.5        |
| PHE        | -57.9±0.2      | 28.8±0.3       | -29.1±0.1       | 12.6±0.0              | 7.3±0.1             | 19.9±0.2          | -9.2±0.1        |
| PRO        | -43.6±1.6      | 20.7±0.8       | -22.9±0.8       | 10.2±0.1              | 5.8±0.0             | 16.0±0.2          | -6.9±0.6        |
| SER        | -52.5±2.2      | 24.5±1.0       | -28.0±1.2       | 9.8±0.1               | 5.8±0.0             | 15.6±0.1          | -12.4±1.1       |
| THR        | -51.7±2.0      | 24.6±1.0       | -27.1±1.1       | 10.6±0.2              | 6.2±0.2             | 16.7±0.4          | -10.3±0.9       |
| TRP        | -65.5±1.0      | 31.7±0.6       | -33.8±0.5       | 14.1±0.1              | 8.3±0.1             | 22.3±0.2          | -11.5±0.4       |
| TYR        | -63.1±3.6      | 30.7±1.5       | -32.4±2.1       | 12.5±0.2              | 7.7±0.1             | 20.2±0.3          | -12.2±1.9       |
| VAL        | -47.5±1.4      | 23.0±0.6       | -24.5±0.8       | 10.8±0.1              | 6.4±0.2             | 17.2±0.3          | -7.3±0.5        |
Table S2: Decomposition of the thermodynamic properties for the TIP4P water model.

| Amino Acid | $\Delta H_{SW}$ | $\Delta H_{WW}$ | $\Delta H_{Solv}$ | $-T\Delta S_{\text{orient}}$ | $-T\Delta S_{\text{trans}}$ | $-T\Delta S_{\text{Solv}}$ | $\Delta G_{\text{Solv}}$ |
|------------|-----------------|-----------------|-------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| ALA        | -46.5±1.1       | 24.4±0.6        | -22.0±0.5         | 10.3±0.1                    | 5.5±0.1                     | 15.8±0.2                    | -6.3±0.4                    |
| ARG(+)     | -127.8±1.6      | 65.0±1.1        | -62.8±0.5         | 15.5±0.1                    | 9.0±0.2                     | 24.5±0.3                    | -38.3±0.4                   |
| ASN        | -68.3±5.6       | 34.8±2.5        | -33.5±3.1         | 13.4±0.5                    | 7.0±0.2                     | 20.4±0.7                    | -13.1±2.5                   |
| ASP(-)     | -145.8±6.9      | 63.1±2.8        | -82.8±4.2         | 20.5±0.1                    | 8.7±0.1                     | 29.2±0.1                    | -53.5±4.1                   |
| CYS        | -49.4±2.1       | 27.1±1.1        | -22.3±1.0         | 10.4±0.2                    | 5.9±0.1                     | 16.3±0.3                    | -6.0±0.8                    |
| GLN        | -70.7±2.0       | 36.0±1.1        | -34.7±0.8         | 14.2±0.1                    | 7.5±0.0                     | 21.7±0.1                    | -12.9±0.8                   |
| GLU(-)     | -151.1±2.7      | 65.2±1.5        | -85.9±1.3         | 21.5±0.2                    | 9.2±0.1                     | 30.6±0.1                    | -55.2±1.1                   |
| GLY        | -46.3±0.3       | 24.7±0.1        | -21.6±0.2         | 9.7±0.0                     | 5.1±0.0                     | 14.8±0.1                    | -6.8±0.2                    |
| HIS        | -71.6±2.2       | 37.1±1.2        | -34.5±1.2         | 14.6±0.3                    | 7.6±0.2                     | 22.2±0.4                    | -12.3±0.8                   |
| HIS(+)     | -114.7±1.2      | 58.6±0.5        | -56.0±0.7         | 14.3±0.2                    | 8.2±0.0                     | 22.5±0.2                    | -33.5±0.7                   |
| ILE        | -53.1±0.8       | 27.6±0.6        | -25.4±0.2         | 12.5±0.0                    | 7.2±0.2                     | 19.7±0.1                    | -5.7±0.2                    |
| LEU        | -53.4±0.8       | 28.5±0.9        | -24.9±0.1         | 12.4±0.1                    | 7.0±0.1                     | 19.4±0.2                    | -5.5±0.1                    |
| LYS(+)     | -129.3±1.6      | 66.3±1.0        | -63.0±0.9         | 15.1±0.2                    | 8.4±0.1                     | 23.5±0.2                    | -39.5±0.7                   |
| MET        | -55.7±2.3       | 30.1±0.7        | -25.7±1.7         | 12.3±0.2                    | 7.1±0.2                     | 19.5±0.3                    | -6.2±1.4                    |
| PHE        | -55.8±3.8       | 30.6±1.7        | -25.2±2.2         | 13.4±0.2                    | 7.6±0.2                     | 20.9±0.4                    | -4.3±1.8                    |
| PRO        | -46.5±1.0       | 24.9±0.4        | -21.6±0.7         | 10.9±0.1                    | 5.8±0.1                     | 16.8±0.2                    | -4.8±0.5                    |
| SER        | -58.4±5.2       | 29.1±2.9        | -29.3±2.7         | 10.8±0.5                    | 5.8±0.3                     | 16.7±0.8                    | -12.7±2.0                   |
| THR        | -55.7±0.9       | 28.6±0.8        | -27.1±0.2         | 11.5±0.1                    | 6.5±0.1                     | 18.0±0.2                    | -9.1±0.2                    |
| TRP        | -70.1±0.6       | 37.8±0.3        | -32.3±0.4         | 15.4±0.1                    | 8.5±0.1                     | 23.9±0.2                    | -8.4±0.3                    |
| TYR        | -67.5±1.1       | 36.3±0.7        | -31.3±0.8         | 13.8±0.3                    | 8.0±0.3                     | 21.9±0.6                    | -9.4±0.3                    |
| VAL        | -51.2±0.4       | 27.0±0.3        | -24.2±0.1         | 11.8±0.1                    | 6.6±0.0                     | 18.4±0.1                    | -5.8±0.1                    |
Table S3: Decomposition of the thermodynamic properties for the TIP5P water model.

| Amino Acid | $\Delta H_{SW}$ | $\Delta H_{WW}$ | $\Delta H_{Solv}$ | $-T\Delta S_{orient}$ | $-T\Delta S_{trans}$ | $-T\Delta S_{Solv}$ | $\Delta G_{Solv}$ |
|------------|----------------|----------------|----------------|---------------------|---------------------|---------------------|----------------|
| ALA        | -41.0±0.9      | 19.7±0.2       | -21.3±0.7      | 9.8±0.1             | 6.0±0.1             | 15.8±0.2             | -5.5±0.5        |
| ARG(+)     | -129.1±2.4     | 57.0±0.6       | -72.1±1.9      | 18.1±0.4            | 11.3±0.2            | 29.4±0.6            | -42.8±1.5       |
| ASN        | -67.2±1.2      | 30.0±0.4       | -37.1±0.9      | 14.2±0.2            | 8.5±0.1             | 22.6±0.3            | -14.5±1.0       |
| ASP(-)     | -123.0±4.9     | 55.9±2.2       | -67.0±2.8      | 16.7±0.1            | 8.6±0.1             | 25.3±0.1            | -41.7±2.7       |
| CYS        | -47.5±3.6      | 23.3±1.7       | -24.2±1.9      | 9.9±0.1             | 6.2±0.1             | 16.1±0.1            | -8.1±1.8        |
| GLN        | -66.3±1.0      | 30.3±0.5       | -35.9±0.5      | 14.6±0.1            | 8.6±0.1             | 23.2±0.2            | -12.7±0.6       |
| GLU(-)     | -126.3±2.4     | 57.7±0.9       | -68.6±1.6      | 17.8±0.0            | 8.7±0.1             | 26.5±0.1            | -42.1±1.6       |
| GLY        | -40.3±0.7      | 19.9±0.7       | -20.5±0.0      | 8.9±0.1             | 5.7±0.0             | 14.6±0.1            | -5.9±0.0        |
| HIS        | -61.3±2.9      | 29.0±0.8       | -32.3±2.1      | 14.0±0.5            | 8.3±0.3             | 22.4±0.8            | -9.9±1.3        |
| HIS(+)     | -112.6±5.4     | 52.4±2.6       | -60.2±2.8      | 15.1±0.5            | 9.2±0.2             | 24.3±0.5            | -35.9±2.3       |
| ILE        | -46.6±1.6      | 22.3±1.1       | -24.4±0.5      | 12.1±0.2            | 7.6±0.3             | 19.7±0.4            | -4.7±0.4        |
| LEU        | -45.5±0.8      | 22.6±0.9       | -22.9±0.3      | 11.5±0.1            | 7.2±0.1             | 18.7±0.2            | -4.2±0.1        |
| LYS(+)     | -127.2±0.9     | 58.3±0.5       | -69.0±0.6      | 16.2±0.1            | 9.4±0.2             | 25.6±0.4            | -43.3±0.3       |
| MET        | -47.9±1.1      | 24.0±0.5       | -23.9±0.7      | 11.7±0.2            | 7.2±0.1             | 18.9±0.2            | -5.0±0.6        |
| PHE        | -52.7±0.6      | 26.1±0.4       | -26.6±0.7      | 12.9±0.3            | 8.1±0.1             | 21.0±0.5            | -5.6±0.2        |
| PRO        | -39.2±0.4      | 19.6±0.2       | -19.6±0.3      | 9.9±0.0             | 6.2±0.1             | 16.1±0.1            | -3.5±0.3        |
| SER        | -55.1±4.2      | 25.0±2.1       | -30.0±2.8      | 10.8±0.9            | 6.3±0.3             | 17.1±1.2            | -12.9±1.5       |
| THR        | -50.7±0.2      | 23.1±0.2       | -27.6±0.4      | 11.4±0.0            | 6.9±0.0             | 18.3±0.0            | -9.4±0.4        |
| TRP        | -58.4±4.0      | 29.3±1.8       | -29.1±2.5      | 14.3±0.4            | 8.8±0.2             | 23.0±0.5            | -6.0±2.0        |
| TYR        | -61.5±3.2      | 28.8±1.6       | -32.7±1.7      | 13.7±0.4            | 8.3±0.2             | 22.0±0.5            | -10.7±1.1       |
| VAL        | -44.0±0.6      | 14.4±10.2      | -22.4±0.3      | 10.9±0.2            | 4.6±3.3             | 17.9±0.3            | -3.0±2.2        |