

# **Minnesota Solvation Database**

**Version 2012**

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## Overview of the Database

The Minnesota Solvation Database – version 2012 (MNSol-v2012) presents a collection of 3037 experimental free energies of solvation or transfer free energies for 790 unique solutes in 92 solvents (including water) and gas-phase M06-2X/MG3S optimized molecular geometries in Cartesian coordinates for the corresponding solutes. All of the 790 solutes in this database (541 neutrals and 249 singly-charged ions) contain at most the following elements: H, C, N, O, F, Si, P, S, Cl, Br, and I.

A set of 3037 free energies of solvation includes several subsets of data described below.

- [a] 274 aqueous free energies of solvation for 274 neutral solutes (including the water dimer) as described in refs 1–3 (the references are given in the final section of the manual)
- [b] 13 aqueous free energies of solvation for 13 neutral solutes as part of a subset of 17 solutes described in refs 4 and 5
- [c] 58 aqueous free energies of solvation for an additional 58 neutral solutes as part of a subset of 63 solutes described in refs 6 and 7
- [d] 26 aqueous free energies of solvation for 26 neutral compounds from SAMPL2 (ref 8)
- [e] 8 aqueous free energies of solvation for 8 iodine-containing hydrocarbons (iodomethane, diiodomethane, iodoethane, 1-iodopropane, 2-iodopropane, 1-iodopentane, 1-iodobutane, and iodobenzene) from ref 9
- [f] 11 aqueous free energies of solvation for 11 neutral compounds from ref 10
- [g] 2140 free energies of solvation for 321 neutral solutes in 90 nonaqueous solvents (232 solutes out of 321 are also included in subset [a], one solute is included in subset [c], 24 solutes are included in subset [d], 8 solutes are included in subset [e], 11 solutes are included in subset [f], and 45 solutes are additional; note also that methanol does not have neutral solutes)<sup>11,12</sup>
- [h] 144 transfer free energies between water and 14 organic solvents for 106 additional neutral solutes<sup>11,12</sup>
- [i] 112 aqueous free energies of solvation for 112 singly-charged ions as described in refs 1–3
- [j] 31 aqueous free energies of solvation for 31 clustered ions containing a single water as described in refs 1–3, 13 (the clustered ions are also included in the unclustered form in a set of 112 ions)
- [k] 220 free energies of solvation in acetonitrile, dimethyl sulfoxide, and methanol for 166 ions as described in refs 2 and 3 (60 ions out of 166 are also included in subset [i], and 106 ions are additional)

## Citation of the Database

If this database is used for published work, the following citation should be given:

Marenich, A. V.; Kelly, C. P.; Thompson, J. D.; Hawkins, G. D.; Chambers, C. C.; Giesen, D. J.; Winget, P.; Cramer, C. J.; Truhlar, D. G. *Minnesota Solvation Database – version 2012*, University of Minnesota, Minneapolis, 2012.

One or more references to the original literature should be given as well. These references are among those given as refs 1–12 in the final section of the manual.

## Contents of the Database

The Minnesota Solvation Database is available for download as a tarred and gzipped file named `MNSolDatabase-v2012.tar.gz`. To open the file, type the commands

```
gunzip MNSolDatabase-v2012.tar.gz
```

```
tar -xvf MNSolDatabase-v2012.tar
```

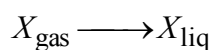
After executing the above commands, a new directory called `MNSolDatabase-v2012` will appear.

The contents of this directory are as follows:

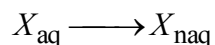
<b>File or directory name</b>	<b>Brief description</b>
<code>MNSol_alldata.xls</code>	a database file in Microsoft Excel format (.xls)
<code>MNSol_alldata.txt</code>	a database file in text (tab delimited) format
<code>all_solutes/</code>	a directory with Cartesian coordinates of all unique solutes
<code>solutes_by_solvent/*/</code>	a directory with Cartesian coordinates of all solutes sorted by solvent

## Description of Experimental Values in the Database

The Minnesota Solvation Database contains two types of free energies: (i) free energies of solvation between the gas phase and the liquid phase and (ii) transfer solvation free energies between water and various nonaqueous solvents. All experimental values in the database are for a temperature of 298 K. The solvation free energies in this database correspond to the following process



where  $X_{\text{gas}}$  is the solute in the gas phase and  $X_{\text{liq}}$  is the solute in the dilute liquid phase. The transfer free energies correspond to the following process



where  $X_{\text{aq}}$  is the solute in the dilute aqueous phase and  $X_{\text{naq}}$  is the solute in a dilute nonaqueous liquid.

Throughout the document, whenever we say free energy of solvation, we mean standard-state free energy of solvation.

### **Standard States**

All of the free energies of solvation in this database are 1 M fixed-concentration standard-state solvation free energies, i.e., they are tabulated using an ideal gas at a concentration of 1 mol/L dissolving as an ideal solution at a concentration of 1 mol/L as the standard state. This standard state is sometimes referred to as the Ben-Naim standard state, and is usually denoted by the superscript “\*”. A commonly used standard state that differs from the one used here is an ideal gas at a concentration of 1 atm dissolving as an ideal solution at a concentration

of 1 mol/L. This standard state is usually denoted by the superscript “o”. The relationship between these two standard states is

$$\Delta G_{\text{gas} \rightarrow \text{liq}}^* = \Delta G_{\text{gas} \rightarrow \text{liq}}^{\text{o}} - \Delta G^{\text{o} \rightarrow *}$$
 (1)

where

$$\Delta G^{\text{o} \rightarrow *} = RT \ln(24.46)$$
 (2)

At 298 K  $\Delta G^{\text{o} \rightarrow *}$  equals 1.89 kcal/mol. Thus, eqs 1 and 2 allow one to convert free energies of solvation in this database, which use a standard state with a gas phase concentration of 1 mol/L and a liquid phase concentration of 1 mol/L, to a standard state that uses a gas phase concentration of 1 atm and a liquid phase concentration of 1 mol/L. All transfer free energies use a standard state concentration of 1 mol/L in both phases, so that the above equations should not be applied to these free energies.

### ***Aqueous Solvation Free Energies of Neutral Solutes***

Most of the aqueous free energies of solvation ( $\Delta G_{\text{S}}^*$ ) in this database were placed on an absolute scale using experimental partition coefficients measured between the gas phase and dilute aqueous solution. The partition coefficient associated with transferring a solute from the gas phase to dilute aqueous solution,  $P_{\text{aq/air}}$ , is related to the free energy of this process by

$$\Delta G_{\text{S}}^* = \Delta G_{\text{aq/air}}^* = -2.303RT \log P_{\text{aq/air}}$$
 (3)

where the “aq/air” denotes transfer from the gas “air” phase, to the dilute aqueous “aq” phase. Also, log is the base 10 logarithm. Example 1 in the “Worked Out Examples” section of this manual shows a sample calculation that uses the above equation.

Some of the aqueous free energies of solvation in this database were determined using experimental values of the dimensionless Henry's Law Constant (HLC), which is the partition coefficient for transferring a solute from dilute aqueous solution to the gas-phase (i.e.,  $P_{\text{air/aq}}$ ). The dimensionless HLC is related to the aqueous solvation free energy according to

$$\Delta G_{\text{S}}^* = 2.303RT \log \text{HLC}(-) \quad (4)$$

where the (-) denotes that the HLC is dimensionless. HLC taken from the PhysProp database (ref 12) are reported in units of  $\text{atm m}^3/\text{mol}$ . These values were converted to dimensionless HLC using the following equation

$$\text{HLC}(-) = \text{HLC} \left( \frac{\text{atm m}^3}{\text{mol}} \right) * \left( 1.218 \times 10^4 \frac{\text{mol K}}{\text{atm m}^3} \right) * \left( \frac{1}{T} \right) \quad (5)$$

where 298 K was used for  $T$ . See example 2 in the "Worked Out Examples" section for a sample calculation that uses eqs 4 and 5.

By assuming ideality, the aqueous solvation free energy can also be expressed in terms of the vapor pressure of the solute in equilibrium with its pure liquid ( $P_{\text{vapor}}$ ) and its aqueous solubility in molarity units ( $S_{\text{aq}}$ ). Some of the aqueous free energies of solvation in the database were determined using (ref 13)

$$\Delta G_{\text{S}}^* = -2.303RT \log \left( \frac{S_{\text{aq}}/M^{\circ}}{P_{\text{vapor}}/P^{\circ}} \right) \quad (6)$$

where  $M^{\circ}$  is equal to 1 mol/L and  $P^{\circ}$  is the pressure (24.45 atm) of an ideal gas at 1 molar concentration and 298 K. See example 3 in the "Worked Out Examples" section for a sample calculation that uses eq 6.



## **Solvation Free Energies of Neutral Solutes in Nonaqueous Solvents**

Several of the experimental solvation free energies of neutral solutes in nonaqueous (organic) solvents that are listed in the database were determined using experimental values of partition coefficients measured between the gas phase and dilute nonaqueous liquids, i.e.

$$\Delta G_S^* = \Delta G_{\text{naq/air}}^* = -2.303RT \log P_{\text{naq/air}} \quad (7)$$

where the “naq/air” denotes that the free energy or partition coefficient is for a solute transferring from the gas phase (“air”) to a dilute nonaqueous liquid (“naq”).

For the most part, nonaqueous free energies of solvation were determined by combining experimental values for the aqueous solvation free energy with experimental partition coefficients measured between the gas phase and dilute nonaqueous liquids, i.e.

$$\Delta G_S^* = \Delta G_{\text{aq/air}}^* - 2.303RT \log P_{\text{naq/aq}} \quad (8)$$

where the “naq/aq” denotes transfer from water to a nonaqueous solvent. (Note that the symbol  $P_{\text{oct}}$  is often used for the special case in which the partition coefficient is measured between water and 1-octanol). Example 4 in the “Worked Out Examples” section uses eq 8.

The database also contains “self solvation” free energies (e.g., the solvation free energy of chloroform solute in pure liquid chloroform). These free energies of solvation were determined using the vapor pressure of the solute in equilibrium with its pure liquid ( $P_{\text{vapor}}$ ) according to

$$\Delta G_S^* = -2.303RT \log \left( \frac{M_{\text{liq}} / M^{\circ}}{P_{\text{vapor}} / P^{\circ}} \right) \quad (9)$$

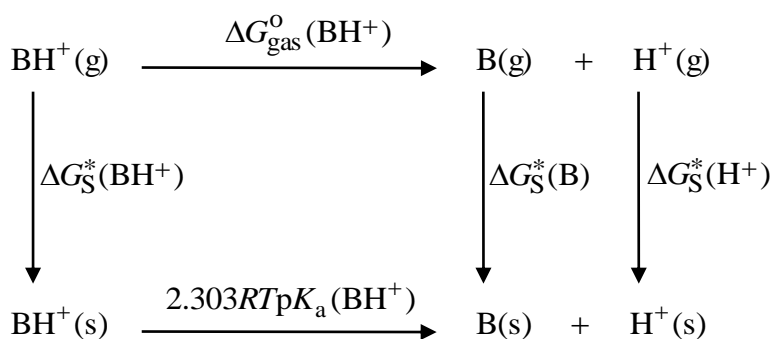
where  $M^0$  is equal to 1 mol/L,  $P^0$  is the pressure (24.45 atm) of an ideal gas at 1 molar concentration and 298 K, and  $M_{\text{liq}}$  is the molarity of the solute in its pure liquid form, which can be calculated from the density of the solute in its pure liquid state and its molecular weight:

$$M_{\text{liq}} = \rho_{\text{liq}} \text{MW}_{\text{liq}} \quad (10)$$

Example 5 in the “Worked Out Examples” section uses eqs 9 and 10.

### **Solvation Free Energies of Ionic Solutes**

The absolute solvation free energy  $\Delta G_{\text{S}}^*(\text{BH}^+)$  of the cation  $\text{BH}^+$  in an arbitrary aqueous or nonaqueous solvent is determined using the thermochemical cycle relating  $\Delta G_{\text{S}}^*(\text{BH}^+)$  to the gas-phase basicity of the base  $B$ :



$$\Delta G_{\text{S}}^*(\text{BH}^+) = \Delta G_{\text{gas}}^0(\text{BH}^+) + \Delta G_{\text{S}}^*(\text{B}) - 2.303RT\text{p}K_{\text{a}}(\text{BH}^+) + \Delta G_{\text{S}}^*(\text{H}^+) + \Delta G^{0 \rightarrow *}$$
 (11)

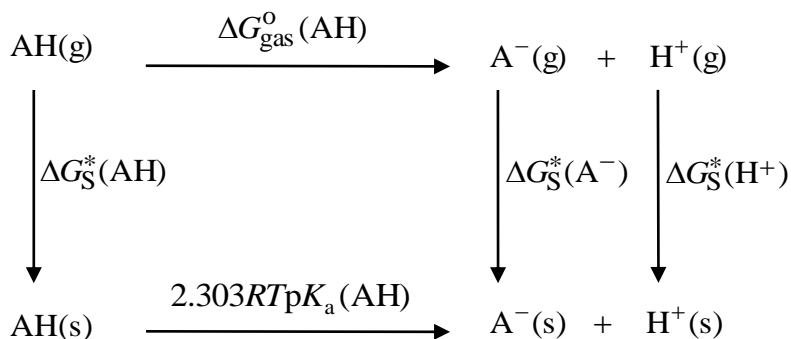
where  $\Delta G_{\text{gas}}^0(\text{BH}^+)$  is the gas-phase acidity of  $\text{BH}^+$ , which is equal to

$$\Delta G_{\text{gas}}^0(\text{BH}^+) = G^0(\text{B}) + G^0(\text{H}^+) - G^0(\text{BH}^+) \quad (12)$$

where  $\Delta G_{\text{S}}^*(\text{B})$  is the solvation free energy of the neutral species  $B$ ,  $\text{p}K_{\text{a}}$  is the negative common logarithm of the solution-phase acid dissociation constant of  $\text{BH}^+$ , and  $\Delta G^{0 \rightarrow *}$  is the free energy

change associated with moving from a gas-phase pressure of 1 atm to a liquid phase concentration of 1 M. See Example 6 in the section entitled “Worked Out Examples”.

Similarly, the absolute solvation free energy  $\Delta G_S^*(A^-)$  of the anion  $A^-$  is determined using the thermochemical cycle relating  $\Delta G_S^*(A^-)$  to the gas-phase acidity of the acid HA:



$$\Delta G_S^*(A^-) = -\Delta G_{\text{gas}}^0(\text{AH}) + \Delta G_S^*(\text{AH}) + 2.303RT\text{p}K_a(\text{AH}) - \Delta G_S^*(\text{H}^+) - \Delta G^{0 \rightarrow *} \quad (13)$$

See Example 7 in the section entitled “Worked Out Examples”.

In the above equations, we use the value of  $-265.9$  kcal/mol for the absolute aqueous solvation free energy of the proton that corresponds to the value of  $-264.0$  kcal/mol reported by Tissandier *et al.* (1998) (the difference is attributed to  $\Delta G^{0 \rightarrow *} = 1.89$  kcal/mol). For the free energies of solvation for the proton in acetonitrile, DMSO, and methanol, we use  $-260.2$ ,  $-273.3$ , and  $-263.5$  kcal/mol, respectively. These solvation energies were evaluated in previous work based on the cluster pair approximation (see Kelly *et al.* (2007)).

For  $F^-$ ,  $Cl^-$ , and  $Br^-$ , we did not use the thermochemical cycles described above. The aqueous solvation free energies of these ions were taken from Tissandier *et al.* (1998) and adjusted for a change in the standard state (see eq 1).

## ***Aqueous Solvation Free Energies of Solute-Water Clusters***

The database includes the aqueous solvation free energy of the water dimer

$$\Delta G_S^*(\text{H}_2\text{O} \cdot \text{H}_2\text{O}) = 2\Delta G_S^*(\text{H}_2\text{O}) - \Delta G_{\text{gas}}^0(\text{B.E.}) + \Delta G^{0 \rightarrow *}_{\text{gas}} + RT \ln(2 \cdot 55.34) \quad (14)$$

where  $\Delta G_S^*(\text{H}_2\text{O})$  is the aqueous solvation free energy of water, and  $\Delta G_{\text{gas}}^0(\text{B.E.})$  is the gas-

phase binding free energy, which equals  $G_{\text{gas}}^0(\text{H}_2\text{O} \cdot \text{H}_2\text{O}) - 2G_{\text{gas}}^0(\text{H}_2\text{O})$ . Substituting

experimental values of  $-6.31$  kcal/mol for  $\Delta G_S^*(\text{H}_2\text{O})$  and  $3.34$  kcal/mol for  $\Delta G_{\text{gas}}^0(\text{B.E.})$  into

eq 14 gives  $-11.27$  kcal/mol for the aqueous solvation free energy of the water dimer.

The aqueous solvation free energies of the 31 solute-water clusters ( $\text{H}_2\text{O} \cdot \text{M}^\pm$ ) were determined according to

$$\Delta G_S^*(\text{H}_2\text{O} \cdot \text{M}^\pm) = \Delta G_S^*(\text{H}_2\text{O}) + \Delta G_S^*(\text{M}^\pm) - \Delta G_{\text{gas}}^0(\text{B.E.}) + \Delta G^{0 \rightarrow *}_{\text{gas}} + RT \ln 55.34 \quad (15)$$

In the above equation, aqueous solvation free energies of the unclustered ions  $\Delta G_S^*(\text{M}^\pm)$  were taken from the database. When available, experimental values for the gas-phase binding energies were used (NIST database). When experimental values were not available, they were calculated at the B97-1/MG3S level of theory. Example 8 in the “Worked Out Examples” section illustrates the use of eq 15.

## ***Transfer Free Energies Between Water and Organic Solvents***

For many solutes, the experimental data required to determine the solvation free energy between the gas and liquid phase are not available. If one were restricted to considering only these free energies of solvation, many solutes important functionality would not be well represented (or not represented at all) in the database. Thus, transfer free energies that were determined using experimental partition coefficients measured between water and various

solvents (i.e.  $P_{\text{naq/aq}}$  values) are also included in the database. The following equation was used to convert experimental partition coefficients into relative free energies of solvation

$$\Delta G_{\text{naq/aq}}^* = -2.303RT \log P_{\text{naq/aq}} \quad (16)$$

### ***Uncertainty of Experimental Data***

The estimated average uncertainty for free energies of solvation and transfer free energies of neutral solutes in subsets [a], [b], [d], [e], [g], and [h] is ~0.2 kcal/mol (refs 1, 5, and 8). The estimated average uncertainty for free energies of solvation in subsets [c] and [f] is about 1 kcal/mol or larger (ref 7). The estimated average uncertainty for solvation free energies of ionic solutes is 3 kcal/mol (ref 1).

## Description of the Database File

The database is distributed in two different forms: (1) as both a portable spreadsheet file, saved as a tab-delimited text file (*MNSol\_alldata.txt*), and (2) as a Microsoft Excel spreadsheet (*MNSol\_alldata.xls*). Each solvation free energy or transfer free energy is one row in the database file, and the pertinent information about each data point is entered in the columns of that row. Below is a listing of the information contained in each of these columns:

<b>column A</b>	Database entry number
<b>column B</b>	File handle for the Cartesian coordinate file of the solute
<b>column C</b>	Name of the solute
<b>column D</b>	Stoichiometric formula of the solute
<b>column E</b>	Solute subset [ <i>a</i> ] through [ <i>k</i> ]
<b>column F</b>	Total charge of the solute
<b>columns G–I</b>	Solute classification numbers. The various solute classes are listed in the “Solute Classification Numbers” section of this manual.
<b>column J</b>	Solvent in which the solvation free energy of the solute is listed
<b>column K</b>	The solvation free energy in kcal/mol
<b>column L</b>	Description of the type of solvation free energy in column K. Solvation free energies are labeled as “abs” and transfer free energies are labeled as “rel”.

The remaining columns are of interest to developers only:

<b>columns M–T</b>	Solvent descriptors for the solvent listed in that row. The eight solvent descriptors (the solvent descriptor $\beta$ appears twice, once as $\beta$ and a second time as $\beta^2$ ) are: $\epsilon$ , dielectric constant at 298 K; $n$ , refractive index at the wavelength of the Na D line; $\alpha$ , the solvent’s hydrogen bond acidity parameter $\Sigma\alpha_2$ ; $\beta$ , the solvent’s hydrogen bond basicity parameter $\Sigma\beta_2$ ; $\gamma$ , macroscopic molecular surface tension in units of cal/mol Å <sup>-2</sup> ; $\phi^2$ , square of the fraction $\phi$ of nonhydrogenic solvent atoms that are aromatic carbon atoms; $\psi^2$ , square of the fraction $\psi$ of nonhydrogenic solvent atoms that are F, Cl, or Br; and $\beta^2$ .
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- columns H–BE** Atomic contributions to the total exposed surface area of a solute molecule, in Å<sup>2</sup>. Exposed surface areas are computed using the ASA algorithm (Liotard, D. A.; Hawkins, G. D.; Lynch, G. C.; Cramer, C. J.; Truhlar, D. G. *J. Comput. Chem.* **1995**, *16*, 422) with a solvent radius of 0.40 Å and Bondi's radii for the corresponding atoms.
- column BF** Total exposed surface area of a solute molecule, in Å<sup>2</sup>. This value is equal to the sum of columns containing atom-wise contributions (such as H, C, O, etc.).

## Version History

### **MNSol Version 2.0 (December 2005)**

**Authors: Kelly, C. P.; Thompson, J. D.; Hawkins, G. D.; Chambers, C. C.; Giesen, D. J.; Winget, P.; Cramer, C. J.; Truhlar, D. G.**

This is the second version of the Minnesota Solvation Database. Parts of this database were taken from an earlier database called “Minnesota Solvation Database Version 2003.1” by Thompson, J. D.; Hawkins, G. D.; Chambers, C. C.; Giesen, D. J.; Winget, P.; Cramer, C. J.; Truhlar, D. G.

### **MNSol Version 2.0.1 (June 2005)**

**Authors: Kelly, C. P.; Thompson, J. D.; Hawkins, G. D.; Chambers, C. C.; Giesen, D. J.; Winget, P.; Cramer, C. J.; Truhlar, D. G.**

The solvent for entry number 1473 (hydrogen peroxide in cyclohexanone) was incorrectly listed as cyclohexane in version 2.0. Version 2.0.1 correctly lists the solvent as cyclohexanone.

In version 2.0 of the database, the chloroform-water solvation free energy for phenylurea was incorrectly listed as  $-0.86$  kcal/mol. Version 2.0.1 lists the correct value of  $+0.86$  kcal/mol for this free energy.

In version 2.0 of the data base, the absolute solvation free energies of hydrazine in benzene, octanol, diethyl ether, and chloroform were based on an older value of  $-9.30$  kcal/mol for the aqueous solvation free energy of hydrazine (this version and previous versions of the data base correctly list  $-6.26$  kcal/mol for the aqueous solvation free energy of hydrazine). In version 2.0.1, the free energies of solvation for hydrazine in the organic solvents above are now correctly computed using a value of  $-6.26$  kcal/mol for the aqueous solvation free energy of hydrazine.

In the geometries directory, *N*-methylaniline is included as a solute twice; once as n012 and another as 0122NMe. The file n012.inp has been removed from this directory, and the listing for n012 has been removed from the files solutes.txt and solutes.xls.

### **MNSol Version 3.0 (January 2007)**

**Authors: Kelly, C. P.; Thompson, J. D.; Hawkins, G. D.; Chambers, C. C.; Giesen, D. J.; Winget, P.; Cramer, C. J.; Truhlar, D. G.**

All of the aqueous solvation free energies of ionic species have been changed from their previous values. Earlier versions of the database used Zhan and Dixon’s value of  $-264.3$  for the absolute aqueous solvation free energy of the proton. This value has been replaced by Tissandier et al.’s value of  $-265.9$  kcal/mol. This change results in the aqueous solvation free energies being shifted by  $+1.6$  kcal/mol for anions and  $-1.6$  kcal/mol for cations relative to the values reported in earlier versions of the database. In previous versions of the database, we determined the



aqueous solvation free energy of  $\text{CH}_2\text{CN}^-$  using a value of 25 for the  $\text{p}K_a$  of acetonitrile. The aqueous solvation free energy of  $\text{CH}_2\text{CN}^-$  is now determined using a more accurate  $\text{p}K_a$  value (28.9) for acetonitrile, resulting in an additional difference of  $-5.3$  kcal/mol. In previous versions of the database, we determined the aqueous solvation free energy of  $(\text{H}_2\text{O})\text{F}^-$  using an incorrect value of  $-12.5$  kcal/mol for the gas-phase clustering free energy of  $\text{F}^-$ . This value has been replaced by the correct value of  $-20.0$  kcal/mol, resulting in an additional difference of  $-7.5$  kcal/mol (which is partially cancelled by the  $+1.6$  kcal/mol difference from above). Finally, in previous versions of the database, we determined the aqueous solvation free energy of  $(\text{H}_2\text{O})\text{H}_3\text{O}^+$

In previous versions of the database, the solutes acetanilide, *p*-cyanoacetanilide, 4-methylacetanilide, and 3-methylacetanilide were included in solute class 3.6.0 (bifunctional H, C, N compounds). All three of these molecules contain amide functionality. *p*-cyanoacetanilide was moved to solute class 4.3 (bifunctional H, C, N, O compounds). 4-methylacetanilide, and 3-methylacetanilide were moved to solute class 4.1.1 (amides).

1-methylthymine has been moved from solute class 4.3 (bifunctional H, C, N, O compounds) to the new solute class, 4.1.4 (thymines).

For nitromethane, previous versions of the database contain free energies of solvation in carbon tetrachloride and cyclohexane, as well as transfer free energies between water and carbon tetrachloride and water and cyclohexane. The two transfer free energies are redundant and were removed.

Using an experimental value for the aqueous solvation free energy of nitromethane, the transfer free energy of nitromethane between octanol and water was converted to a solvation free energy. Similarly, the transfer free energies of 3,5-dimethylpyridine between benzene and water, 4-ethylpyridine between octanol and water,  $\gamma$ -butyrolactone between octanol and water, pyrrole between chloroform and water, octanol and water, and cyclohexane and water, and quinoline between chloroform and water, octanol and water, and cyclohexane and water, were converted to free energies of solvation in the above organic solvents using experimental values for the aqueous solvation free energies of these solutes.

Experimental partition coefficients and experimental aqueous free energies of solvation were used to add 80 free energies of solvation in organic solvents for the following 14 solutes: hydrogen peroxide, urea, benzamide, methylhydrazine, 2-methylaniline, 3-methylaniline, 4-methylaniline, *N*-methylaniline, *N*-methyl-2-pyrrolidinone, 2-pyrrolidinone, formamide, *N,N*-dimethylformamide, *N*-methylformamide, and *N,N*-dimethylacetamide.

63 relative free energies of solvation between water and organic solvents for an additional 31 solutes, the majority of which contain amide groups, were also added.

### **MNSol Version 2009 (March 2009)**

**Authors: Marenich, A. V.; Kelly, C. P.; Thompson, J. D.; Hawkins, G. D.; Chambers, C. C.; Giesen, D. J.; Winget, P.; Cramer, C. J.; Truhlar, D. G.**

Two hundred twenty free energies of solvation for 166 unique ions in acetonitrile, dimethyl sulfoxide, and methanol have been added to the database. While 60 ions out of 166 were previously included in a set of 112 aqueous ions, the remaining 106 ions are new.

Thirteen neutral solutes in water from the SAMPL0 training set (Nicholls, A.; Mobley, D. L.; Guthrie, J. P.; Chodera, J. D.; Bayly, C. I.; Cooper, M. D.; Pande, V. S. *J. Med. Chem.* **2008**, *51*, 769) have been added to the database. Note that the aforementioned paper describes 17 aqueous solutes, four of which (benzyl bromide, benzyl chloride, 1,4-dioxane, and diethyl sulfide) are already in a subset of 274 aqueous neutral data.

Fifty eight aqueous solutes from the SAMPL1 training set (Guthrie, J. P. *J. Phys. Chem. B* **2009**, in press) have also been added. Note that the aforementioned paper describes 63 aqueous solutes, two of which (cup08062 and cup08042) have been excluded from consideration by the reason explained in Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. A* **2009** (in press). The other three compounds out of 63 (fenuron, dichlobenil, and methyl parathion) are not in the set of 58 compounds because they were previously included in a subset of 274 aqueous data.

It has been reported recently (Bryantsev, V. S.; Diallo, M. S.; Goddard, W. A., III. *J. Phys. Chem. B* **2008**, *112*, 9709) that the equations previously used to calculate the solvation free energies of the water dimer and solute-water clusters (eqs 4 and 8 in Kelly, C. P.; Cramer, C. J.; Truhlar, D. G. *J. Chem. Theory Comput.* **2005**, *1*, 1133) miss the concentration correction terms that are the last terms in eqs 14 and 15 in the present manual. Thus the previously reported aqueous solvation energies of the water dimer and the clustered ions in the database have been corrected by 2.79 and 2.38 kcal/mol, respectively, for the water dimer and the ion-water cluster to account for this error.

### **MNSol Version 2012 (November 2012)**

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The present version of MNSol containing 3037 reference solvation data improves on the earlier version (MNSol-v2009) containing 2923 data in two ways: (i) solutes molecular geometries were re-optimized using a more accurate density functional and a larger basis set (namely, M06-2X/MG3S) whereas the MNSol-v2009 geometries were optimized using mPW1PW/MIDI! and HF/MIDI!; (ii) we added 131 new solvation data to MNSol-v2009 and removed 17 old data that became redundant in the new database. Subsets [a], [b], [c], [i], [j], and [k] in MNSol-v2012 are the same as in MNSol-v2009. Subsets [d], [e], and [f] are new. Subset [g] in the older database contains 2072 solvation data, to which we have added 57 new data described in more detail in ref 11 plus 11 solvation free energies in *n*-octanol for 11 solutes from ref 10 obtained from the reference solvation energies in water<sup>10</sup> and the reference octanol–water partition coefficients<sup>12</sup> for these compounds. Recent modifications to subset [h] are described in ref 11.

## Solute Classification Numbers

1. H<sub>2</sub>, NH<sub>3</sub>, and H<sub>2</sub>O
  - 1.1 H<sub>2</sub>
  - 1.2 NH<sub>3</sub>
  - 1.3 H<sub>2</sub>O
  
2. Compounds containing H and/or C and O
  - 2.1. Hydrocarbons
    - 2.1.1. Unbranched alkanes
    - 2.1.2. Branched alkanes
    - 2.1.3. Cycloalkanes
    - 2.1.4. Alkenes
    - 2.1.5. Alkynes
    - 2.1.6. Arenes
  - 2.2. Simple hydroxyl compounds
    - 2.2.1. Alcohols
    - 2.2.2. Phenols
  - 2.3. Ethers
  - 2.4. Aldehydes and Ketones
    - 2.4.1. Aldehydes
    - 2.4.2. Ketones
  - 2.5. Carboxylic acids
  - 2.6. Esters
  - 2.7. Lactones
  - 2.8. Peroxides
  - 2.9. Bifunctional H, C, O compounds
  
3. Compounds containing H and/or C and N
  - 3.1. Aliphatic amines
  - 3.2. Anilines
  - 3.3. Aromatic nitrogen heterocycles
    - 3.3.1. 1 nitrogen in the ring
    - 3.3.2. 2 nitrogens in the ring
  - 3.4. Nitriles
  - 3.5. Hydrazines
  - 3.6. Bifunctional H, C, N compounds
  
4. Compounds containing H, C, N, and O
  - 4.1. Amides and ureas
    - 4.1.1. Amides
    - 4.1.2. Ureas
    - 4.1.3. Lactams
    - 4.1.4. Thymines (uracils)
  - 4.2. Nitrohydrocarbons
  - 4.3. Bifunctional H, C, N, O compounds

5. Compounds containing H, C, and F
  - 5.1. Fluoroalkanes
  - 5.2. Fluoroarenes
6. Compounds containing H, C, and Cl
  - 6.1. Chloroalkanes
  - 6.2. Chloroalkenes
  - 6.3. Chloroarenes
7. Compounds containing H, C, and Br
  - 7.1. Bromoalkanes
  - 7.2. Bromoalkenes
  - 7.3. Bromoarenes
8. Multihalogen hydrocarbons
9. Halogenated bifunctional compounds, containing at most H, C, N, O, F, Cl, Br
  - 9.1. Bifunctional halogen compounds containing O
  - 9.2. Bifunctional halogen compounds containing N
  - 9.3. Bifunctional halogen compounds containing N and O
10. Compounds containing S, but not P
  - 10.1. Thiols
  - 10.2. Sulfides
  - 10.3. Disulfides
  - 10.4. Sulfur heterocycles
  - 10.5. Non-halogenated sulfur-containing bifunctional compounds
  - 10.6. Halogenated sulfur-containing compounds
  - 10.7. Sulfoxides
11. Phosphorus compounds
  - 11.1. Compounds containing at most H, C, N, O and P
  - 11.2. Nonhalogenated P compounds containing S
  - 11.3. Halogenated P compounds not containing S
  - 11.4. Halogenated P compounds containing S
12. Silicon compounds
  - 12.1. Compounds containing H, C, and Si
  - 12.2. Compounds containing H, C, O, and Si
13. Ionic compounds
  - 13.1. Ions containing only H and C
  - 13.2. Ions containing only H, C and O
  - 13.3. Ions containing only H, C, and N
  - 13.4. Ions containing only H, C, N, and O
  - 13.5. Ions containing S
  - 13.6. Halogenated ions
  - 13.7. Inorganic ions
14. Solute-water clusters
  - 14.1. Neutrals
  - 14.2. Ions
15. Iodine compounds

## Worked Out Examples

### Example 1: Aqueous solvation free energy from the water/air partition coefficient

The experimental aqueous solvation free energy of anisole is listed as  $-2.45$  kcal/mol in the database. This value was determined using an experimental  $\log P_{\text{aq/air}}$  value of 1.80, which was taken from Abraham et al. (1990):

$$\Delta G_{\text{S}}^* = -2.303RT \log P_{\text{aq/air}}$$

$$\Delta G_{\text{S}}^* = -2.303 \left( 1.987 \times 10^{-3} \frac{\text{kcal}}{\text{mol K}} \right) * (298 \text{ K}) * (-1.80) = -2.45 \text{ kcal/mol}$$

### Example 2: Aqueous solvation free energy from the Henry's Law Constant

The experimental aqueous solvation free energy of benzamide is listed as  $-10.90$  kcal/mol in the database. This value was determined using an experimental HLC of  $2.45\text{E-}10$  atm m<sup>3</sup>/mol, which was taken from the PhysProp database:

Part 1:

$$\text{HLC}(-) = \text{HLC} \left( \frac{\text{atm m}^3}{\text{mol}} \right) * \left( 1.218 \times 10^4 \frac{\text{mol K}}{\text{atm m}^3} \right) * \left( \frac{1}{T} \right)$$

$$\text{HLC}(-) = 2.45 \times 10^{-10} \left( \frac{\text{atm m}^3}{\text{mol}} \right) * \left( 1.218 \times 10^4 \frac{\text{mol K}}{\text{atm m}^3} \right) * \left( \frac{1}{298 \text{ K}} \right) = 1.00 \times 10^{-8}$$

Part 2:

$$\Delta G_{\text{aq/air}}^* = 2.303RT \log \text{HLC}(-)$$

$$\Delta G_{\text{aq/air}}^* = 2.303 \left( 1.987 \times 10^{-3} \frac{\text{kcal}}{\text{mol K}} \right) * (298 \text{ K}) * (-8.00) = -10.90 \text{ kcal/mol}$$

### Example 3: Aqueous solvation free energy from vapor pressure and solubility

The experimental aqueous solvation free energy of urea is listed as  $-13.80$  kcal/mol in the database. This value was determined using an experimental  $S_{\text{aq}}$  value of  $8.99$  mol/L and an experimental  $P_{\text{vapor}}$  value of  $1.579 \times 10^{-8}$  atm, which were both taken from the PhysProp database:

$$\Delta G_{\text{S}}^* = -2.303RT \log \left( \frac{S_{\text{aq}}/M^{\circ}}{P_{\text{vapor}}/P^{\circ}} \right)$$

$$\Delta G_{\text{S}}^* = -2.303 \left( 1.987 \times 10^{-3} \frac{\text{kcal}}{\text{mol K}} \right) * (298 \text{ K}) * \log \left( \frac{8.99 \text{ mol/L} / 1.0 \text{ mol/L}}{1.579 \times 10^{-8} \text{ atm} / 24.45 \text{ atm}} \right) = -13.80 \text{ kcal/mol}$$

### Example 4: Solvation free energy in an organic liquid from the aqueous solvation free energy and the organic liquid - water partition coefficient

The experimental solvation free energy for phenol in octanol is listed as  $-8.69$  kcal/mol in the database. This value was determined using an experimental value of  $-6.62$  kcal/mol for the aqueous solvation free energy of phenol, which was taken from the database, and an experimental value of  $1.52$  for  $\log P_{\text{naq/oaq}}$ , which was taken from the MedChem database:

$$\Delta G_{\text{S}}^* = \Delta G_{\text{aq/air}}^* - 2.303RT \log P_{\text{naq/oaq}}$$

$$\Delta G_{\text{S}}^* = -6.62 \text{ kcal/mol} - 2.303 \left( 1.987 \times 10^{-3} \frac{\text{kcal}}{\text{mol K}} \right) * (298 \text{ K}) * 1.52 = -8.69 \text{ kcal/mol}$$

### Example 5: Solvation free energy in an organic liquid from the vapor pressure of the solute over its pure liquid

The experimental self-solvation free energy of carbon tetrachloride (i.e. carbon tetrachloride in carbon tetrachloride) is listed as  $-4.35$  kcal/mol in the database. To calculate the molarity ( $M_{\text{liq}}$ ) of pure carbon tetrachloride, the density of carbon tetrachloride ( $1.5842$  g/mL, which equals  $10.30$  mol/L) and its molecular weight ( $153.2$  g/mol) were used in eq 10. An experimental value of  $0.151$  atm was used for the vapor pressure of carbon tetrachloride in equilibrium with its pure liquid ( $P_{\text{vapor}}$ ), which was taken from the *CRC Handbook*:

$$\Delta G_{\text{S}}^* = -2.303RT \log\left(\frac{M_{\text{liq}}/M^{\circ}}{P_{\text{vapor}}/P^{\circ}}\right)$$

$$\Delta G_{\text{S}}^* = -2.303 * \left(1.987 \times 10^{-3} \frac{\text{kcal}}{\text{mol K}}\right) * (298 \text{ K}) \log\left(\frac{10.30 \text{ mol/L} / 1 \text{ mol/L}}{0.151 \text{ atm} / 24.45 \text{ atm}}\right) = -4.35 \text{ kcal/mol}$$

### Example 6: Aqueous solvation free energy of methylammonium ( $\text{CH}_3\text{NH}_3^+$ )

The experimental aqueous solvation free energy of methylammonium is listed as  $-76.4$  kcal/mol in the database. This value was determined using the data shown below:

	Experimental Value	Ref.
$\Delta G_{\text{gas}}^{\circ}(\text{BH}^+)$	206.6 kcal/mol	NIST
$\Delta G_{\text{S}}^*(\text{B})$	$-4.56$ kcal/mol	MNSol1.1
$\text{p}K_{\text{a}}(\text{BH}^+)$	10.6	Stewart (1985)
$\Delta G_{\text{S}}^*(\text{H}^+)$	$-265.9$ kcal/mol	Tissandier et al. (1998)
$\Delta G^{\circ \rightarrow *}$	1.89 kcal/mol	–

$$\Delta G_{\text{S}}^*(\text{BH}^+) = \Delta G_{\text{gas}}^{\circ}(\text{BH}^+) + \Delta G_{\text{S}}^*(\text{B}) - 2.303RT \text{p}K_{\text{a}}(\text{BH}^+) + \Delta G_{\text{S}}^*(\text{H}^+) + \Delta G^{\circ \rightarrow *} = -76.4 \text{ kcal/mol}$$

**Example 7: Aqueous solvation free energy of methoxide (CH<sub>3</sub>O<sup>-</sup>)**

The experimental aqueous solvation free energy of methoxide is listed as -95.0 kcal/mol in the database. This value was determined using the data shown below:

	Experimental Value	Ref.
$\Delta G_{\text{gas}}^{\circ}(\text{AH})$	375.0 kcal/mol	NIST
$\Delta G_{\text{S}}^*(\text{AH})$	-5.11 kcal/mol	MNSol1.1
$\text{p}K_{\text{a}}(\text{AH}^+)$	15.5	Stewart (1985)
$\Delta G_{\text{S}}^*(\text{H}^+)$	-265.9 kcal/mol	Tissandier et al. (1998)
$\Delta G^{\circ \rightarrow *}$	1.89 kcal/mol	-

$$\Delta G_{\text{S}}^*(\text{A}^-) = -\Delta G_{\text{gas}}^{\circ}(\text{AH}) + \Delta G_{\text{S}}^*(\text{AH}) + 2.303RT\text{p}K_{\text{a}}(\text{AH}) - \Delta G_{\text{S}}^*(\text{H}^+) - \Delta G^{\circ \rightarrow *} = -95.0 \text{ kcal/mol}$$

**Example 8: Aqueous solvation free energy of methoxide + 1H<sub>2</sub>O [H<sub>2</sub>O(CH<sub>3</sub>O)<sup>-</sup>]**

The experimental aqueous solvation free energy of the methoxide-water cluster is listed as -80.0 kcal/mol in the database. This value was determined using the data shown below:

	Experimental Value	Ref.
$\Delta G_{\text{S}}^*(\text{H}_2\text{O})$	-6.31 kcal/mol	MNSol1.1
$\Delta G_{\text{S}}^*(\text{M}^{\pm})$	-95.0 kcal/mol	MNSol1.1
$\Delta G_{\text{gas}}^{\circ}(\text{B.E.})$	-17.00 kcal/mol	NIST
$\Delta G^{\circ \rightarrow *}$	1.89 kcal/mol	-
$RT \ln 55.34$	2.38 kcal/mol	-

$$\Delta G_{\text{S}}^*(\text{H}_2\text{O} \cdot \text{M}^{\pm}) = \Delta G_{\text{S}}^*(\text{H}_2\text{O}) + \Delta G_{\text{S}}^*(\text{M}^{\pm}) - \Delta G_{\text{gas}}^{\circ}(\text{B.E.}) + \Delta G^{\circ \rightarrow *} + RT \ln 55.34 = -80.0 \text{ kcal/mol}$$



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