

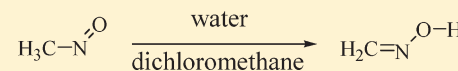
## Combined ab Initio/DFT and Monte Carlo Calculation of Relative Standard Chemical Potentials in Solution

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Supporting Information

**ABSTRACT:** A method has been proposed for pure theoretical estimation of relative standard chemical potentials (1 mol/dm<sup>3</sup> standard state) and related  $K_c$  equilibrium constants for tautomers/conformers dissolved in some solvents. The relative internal free energy could be obtained by means of in-solution ab initio/DFT methods. Using the free energy perturbation method for the transformation of the involved species, the solvation contribution to the relative standard chemical potential can be determined by considering 1 M solution models. Comparison of the  $\Delta G_{\text{solv}}/\text{MC}$  value calculated for the 1 M solution with those obtained for the system at other concentrations helps explore the ratio of the activity coefficients in nonstandard states. The method has been applied for the study of the tautomeric pair of formaldoxime and nitrosomethane with large structural differences. It was pointed out that the  $\Delta G_{\text{solv}}/\text{MC}$  values for the 1 and 0.11 M solutions differ by up to 0.2 kcal/mol, when atomic charges are derived on the basis of the in-solution IEF-PCM/B3LYP/aug-cc-pvtz molecular electrostatic potential. On the basis of calculated free energy differences, the ratio of the  $\text{CH}_3\text{NO}$  and  $\text{CH}_2\text{NOH}$  activity coefficients in 0.11 molar aqueous and dichloromethane solutions were predicted as of 1.4 and 0.8, respectively. The 0.11 M model is hypothetical by assuming that only one of the tautomers exists in the solution box. As an extension of the method, a procedure has been outlined where contributions to the change of the solvation free energy by terms related to relative activity coefficients might be assessed at physically relevant concentrations for the equilibrated tautomers.



## INTRODUCTION

The equilibrium constant for a chemical process is defined as  $-RT \ln K = \sum_i \nu_i \mu_i^0$ , where  $\mu_i^0$  is the standard chemical potential of the  $i$ th component of the reaction and  $\nu_i$  is the corresponding stoichiometric coefficient, negative for the reactants. From computational point of view, however, a suitable definition of the standard chemical potential in solution is difficult. In the classical derivation of the  $\mu_i$  chemical potential for real, dilute solutions,<sup>1</sup>  $\mu_i$  was provided with reference to a hypothetical standard state. Such a reference state is not feasible for theoretical approaches, and an alternative formulation was proposed recently<sup>2</sup> considering the 1 molar solution as the standard state

$$\mu_i(c_i) = \mu_i^0 + RT \ln \gamma_i(c_i)(c_i/c_0) \quad (1a)$$

Here  $c_i$  is the solute concentration,  $\gamma_i(c_i)$  is the related activity coefficient, and  $c^0 \equiv 1 \text{ mol/dm}^3$  is the unit chemical concentration making the argument of the logarithmic term dimensionless. Using the definition equation in ref 2,  $\gamma_i = 1$  when  $c_i = c_0 = 1$ , letting  $\mu_i(c_i = 1) = \mu_i^0$ . The consequence of setting the 1 molar solution to the standard state is that the  $\gamma_i$  coefficients do not converge to unity for an infinitely dilute solution, in contrast to the formulation when the composition is characterized by the molar fraction.<sup>1</sup>

The standard potential can be divided into internal and solvation-related parts as  $\mu_i^0 = \mu_i^0(\text{int}) + \mu_i^0(\text{solv})$ , and  $\mu_i(c_i)$  can be defined then as the sum of the  $\mu_i^0(\text{int})$  and  $\mu_i(\text{solv}, c_i)$  contributions

$$\begin{aligned} \mu_i(c_i) &= \mu_i^0(\text{int}) + (\mu_i^0(\text{solv}) + RT \ln \gamma_i(c_i)(c_i/c_0)) \\ &= \mu_i^0(\text{int}) + \mu_i(\text{solv}, c_i) \end{aligned} \quad (1b)$$

Using eq 1a for expressing the individual chemical potentials in the solution, the  $K$  equilibrium constant (depending now on concentration and denoted by  $K_c$ ) is provided as

$$K_c = \prod (\gamma_i(c_i)(c_i/c_0))^{\nu_i} \quad (2)$$

For the simplest  $m \leftrightarrow n$  equilibrium,  $K_c = \gamma_n c_n / \gamma_m c_m$  and eq 3 applies

$$\begin{aligned} -RT \ln K_c &= (\mu_n^0(\text{int}) - \mu_m^0(\text{int})) + (\mu_n^0(\text{solv}) - \mu_m^0(\text{solv})) \\ &= \Delta \mu^0(\text{int}) + \Delta \mu^0(\text{solv}) \end{aligned} \quad (3)$$

The  $\Delta \mu^0(\text{int})$  term can be determined by in-solution ab initio or DFT calculations for one mole of the reactants (see the Methods and Calculations section). Determination of the  $\Delta \mu^0(\text{solv})$  term is the main subject of the present paper.

The Gibbs function,  $G(X)$ , of a system  $X$  ( $X = A, B$ ) composed of  $n_{\text{su}}$  solute and  $n_{\text{sv}}$  solvent molecules is<sup>1</sup>

$$G(X) = n_{\text{su}}(X)\mu_{\text{su}}(X) + n_{\text{sv}}(X)\mu_{\text{sv}}(X) \quad (4)$$

If the composition is equal for the systems A and B, thus  $n_{\text{su}}(A) = n_{\text{su}}(B)$  and  $n_{\text{sv}}(A) = n_{\text{sv}}(B)$  then

$$\begin{aligned} \Delta G &= G(B) - G(A) \\ &= n_{\text{su}}[\mu_{\text{su}}(B) - \mu_{\text{su}}(A)] + n_{\text{sv}}[\mu_{\text{sv}}(B) - \mu_{\text{sv}}(A)] \end{aligned} \quad (5)$$

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By assuming that the  $n_{sv}(X)\mu_{sv}(X)$  term is equal for the solvent in the two systems up to 1 M solution concentration, then  $\Delta G = n_{su}[\mu_{su}(B) - \mu_{su}(A)]$ . For a system including  $n_{su}$  solute molecules in a molar solution model, where  $\gamma_n = \gamma_m = 1$  and  $c_n = c_m = 1$ ,  $\Delta G/n_{su} = \Delta\mu^0$ . In a model with  $n_{su} = 1$

$$\begin{aligned}\Delta G &= \mu_n^0(B) + RT \ln[\gamma_n(c_n/c^0)]_B - \mu_m^0(A) - RT \ln[\gamma_m(c_m/c^0)]_A \\ &= \Delta\mu^0 + RT \ln[(\gamma_n c_n)_B / (\gamma_m c_m)_A] \\ &= \Delta\mu^0(int) + \Delta\mu^0(solv) + RT \ln[(\gamma_n c_n)_B / (\gamma_m c_m)_A] \quad (6a)\end{aligned}$$

with

$$\Delta G_{solv} = \Delta\mu^0(solv) + RT \ln[(\gamma_n c_n)_B / (\gamma_m c_m)_A] \quad (6b)$$

It is impossible to ensure conditions for any real chemical system in thermodynamic equilibrium that compounds only from the reactant or the product side would be present. The free energy perturbation method as implemented into Monte Carlo simulations provides, however, a theoretical tool to compose solution models including only the “m” or the “n”-type molecules in the model system. Then, using a nonphysical pathway, compound “m” can be gradually transformed into compound “n”. By this way, calculation of  $\Delta\mu^0(solv)$  is possible, because the free energy is a state function, whose change depends only on the difference of the  $\mu^0$  values for the systems at the beginning and the end of the simulation.

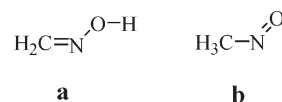
Thus whereas the procedure proposed here cannot determine the  $\mu^0(solv)$  values by themselves, their change is enough for the theoretical determination of  $K_c$  if  $\Delta\mu^0(int)$  is calculated separately. The only thing to do is calculate the variation of the solvation free energy for molar solution models with solutes “m” and “n”. This may be, however, a very time-consuming procedure.

In an early attempt, the author calculated the electrostatic part of the free energy of the hydration for the solute  $\text{MeNH}_2$ .<sup>3</sup> The procedure was conducted by uncharging the atoms of the single solute in a box of 504 water molecules. The model system corresponded to an infinitely dilute solution. However, because the standard state is the molar solution, a 1 mol/dm<sup>3</sup> model including nine  $\text{MeNH}_2$  solutes were also considered, and the uncharging procedure was repeated in a very long simulation for the nine solutes. The calculated average contribution by one of the nine solutes to the total free energy change did not differ significantly from the value obtained through the uncharging of a single solute in the infinitely dilute solution. It was concluded that, for very small organic solutes, consideration of the dilute solution is satisfactory.

Recent simulations for larger solutes having 4–7 C, N, and O atoms and hydrogens<sup>2,4–6</sup> indicate, however, partial association in 0.2–1 M solutions. An association on microscale was defined as remarkably shorter distances for reference atoms than calculated from the uniform distribution in accord with the overall concentration.<sup>6</sup> This solution-structure characteristic must be a feature of the stable thermodynamic state, but it cannot be modeled in dilute solutions with only 1–2 solutes.

The aim of this paper is to present a simulation procedure for estimating relative standard chemical potentials in solution. If the predicted change of the solvation free energy per mole differs on the basis of calculations for 0.11 and 1 M solutions, the role of the relative activity coefficients could be assessed in nonstandard states. The formaldoxime-nitrosomethane tautomeric pair was selected in order to avoid parallel conformational equilibria and keeping the solute molecule as small as possible in a real tautomeric system. A further goal in the solute selection was to consider compounds where the dipole moment largely changes; so

**Scheme 1.** *trans*-Formaldoxime (a) and Nitrosomethane (b)



a remarkable calculated difference may be expected in polar solvents as water and dichloromethane. The internal energy changes were calculated up to the B3LYP/aug-cc-pvtz and QCISD(T)/CBS levels in the two solvents.

## METHODS AND CALCULATIONS

Details of the quantum mechanical calculations carried out by means of the Gaussian 03 package<sup>7</sup> running at the Ohio Supercomputer Center were described in recent publications.<sup>8,9</sup> Molecular geometries for the tautomers (Scheme 1) were optimized at the DFT/B3LYP/6-31G\* level,<sup>10,11</sup> both in the gas phase and in solution. Polarizable continuum dielectric studies in water, methanol and dichloromethane with dielectric constants  $\epsilon = 78.39$ , 32.61, and 8.32, respectively, were performed by using the PCM approach in its integral-equation formalism.<sup>12–17</sup> Cavities were created considering scaled Bondi radii.<sup>18,19</sup> Single-point B3LYP energies were calculated using the aug-cc-pvtz basis set.<sup>20–22</sup>

$\Delta\mu^0(int)$  was accepted as independent of the solute concentration and was calculated as  $\Delta E_{int} + \Delta G_{th(ermal)}$  for the formaldoxime and nitrosomethane solutes.  $E_{int}$  is equal to  $\langle \Psi | H | \Psi \rangle$  in a DFT calculation (at the considered basis set), wherein  $H$  is the solute's Hamiltonian and  $\Psi$  is the converged wave function of the solute obtained from the in-solution calculation. In ab initio calculations, the  $\langle \Psi | H | \Psi \rangle$  SCF energy was corrected by the E2 term in MP2 calculations.

The QCISD(T)<sup>23</sup> complete basis set relative energy,  $\Delta E_{CBS}^{QCISD(T)}$  was calculated as follows:

$$\Delta E_{CBS}^{QCISD(T)} = \Delta E_{CBS}^{MP2} + (\Delta E_{CBS}^{QCISD(T)} - \Delta E_{aug-cc-pvdz}^{MP2}) \quad (7)$$

$\Delta E_{CBS}^{MP2}$  values were calculated by using the extrapolation method of Helgaker et al.<sup>24,25</sup> Single-point calculations were carried out applying the aug-cc-pvdz and aug-cc-pvtz basis sets. Eventually,  $\Delta\mu^0(int)$  was set to  $\Delta E_{CBS}^{QCISD(T)} + \Delta G_{th}$  in a given solvent, where the latter relative thermal correction was calculated at  $T = 298$  K and  $p = 1$  atm in the rigid-rotor, harmonic oscillator approximation.<sup>26</sup>

Monte Carlo (MC) simulations in isobaric–isothermal ensembles<sup>27–29</sup> (NpT) at  $p = 1$  atm and  $T = 298$  K were performed by utilizing the BOSS 4.8 software package.<sup>30</sup> The box sizes were chosen in order to keep up edges of 24.63 Å, corresponding to 9 dm<sup>3</sup> solution volumes considering  $N_A = 6.02205 \times 10^{23}$  boxes. Accordingly, 470 and 500 TIP4P water molecules<sup>31</sup> and 133 and 150 dichloromethane solvent molecules were considered (lower numbers for the molar model). The desired volumes were kept up within about  $\pm 1\%$ . Models of about 0.11 molar and one molar solutions considered a single solute and nine solute molecules in a solvent box, respectively. For the dichloromethane (DCM) solution, the three-point model of  $\text{CH}_2\text{Cl}_2$  by Lim et al. was utilized.<sup>32</sup> Periodic boundary conditions and preferential sampling were applied, and the intermolecular interactions were calculated by the all-atom OPLS-AA 12-6-1 force field.<sup>33,34</sup> The 12-6 Lennard-Jones parameters were taken from the program's library, whereas net atomic charges were fitted by the CHELPG procedure<sup>35</sup> to the molecular electrostatic potential (ELPO), calculated

at the IEF-PCM/B3LYP level using the 6-31G\* and aug-cc-pvtz basis sets. For comparison, in-solution B3LYP/6-311++G\*\*, MP2/aug-cc-pvdz, and MP2/aug-cc-pvtz ELPO-fitted charges are also presented. Solute–solvent and solvent–solvent cutoffs were set to 12 Å. Solute–solute interactions were calculated at any solute separation for the molar model by applying the minimum image convention. Long-range electrostatic effects were considered by means of Ewald summation.<sup>36,37</sup> Volume changes up to about 2% were allowed in every 1000th step. Solute moves were attempted in every 50 steps for the 0.11 molar model. Movement of a randomly chosen solute molecule was attempted in every 10th step for the molar model. Acceptance ratio of a new configuration was in the range of 40–60%.

The tautomers were transformed into each other along a nonphysical path. The proton of the hydroxy group in CH<sub>2</sub>NOH was gradually annihilated and the third hydrogen connecting to the carbon atom in CH<sub>3</sub>NO was gradually developed. The perturbation calculations used the FEP method<sup>38,39</sup> as implemented into the BOSS.4.8 package. The geometric and OPLS parameters were transformed into each other by applying a linear coupling parameter,  $\lambda$ . Appropriate choice of  $\Delta\lambda$  through the FEP calculations is a key issue. In order to keep the dG solvation free energy increments below 1 kcal/mol,  $\Delta\lambda$  was accepted up to 0.1 for the 0.11 molar solutions. For the molar models,  $\Delta\lambda$  was chosen in the range of 0.0015–0.075. By this coupling and applying double-wide sampling,<sup>30</sup> CH<sub>2</sub>NOH was transformed into CH<sub>3</sub>NO in 13 steps (DCM) and 28 steps (water).

At every reference point, 7.5 million (M) configurations were considered in each of the equilibration and averaging phase for the 0.11 M model. For the molar model, 45 and 30 M configurations were considered for the equilibration and averaging, respectively, at every reference point. Final dG solvation free energy increments were obtained upon averaging data over the last 30 M configurations. The above choices of  $\Delta\lambda$  and the lengths of the equilibration and averaging phases led to standard deviations for the solvation free energy differences up to 0.11 kcal/mol for the total FEP procedures.

## RESULTS AND DISCUSSION

**Relevance of the B3LYP/6-31G\* Optimization.** For the structure determination of a solute in a solvent by applying the PCM method, three factors have to be considered: the level of the theory used for the structure determination, the applied basis set, and the cavity model. If the resulting molecular electrostatic potential is used in a fitting process to assign atomic charges, the fitting process is a fourth variable for preparing input data for Monte Carlo simulations characterized above.

B3LYP/6-31G\* optimizations provided structural parameters agreeing well with the experimental values for the gas-phase CH<sub>3</sub>NH<sub>2</sub>, aniline, phenol,<sup>40</sup> imidazole,<sup>41</sup> methanol,<sup>42</sup> (CH<sub>3</sub>)<sub>3</sub>N, and pyridine.<sup>9</sup> The QCISD(T)<sub>CBS</sub>/B3LYP/6-31G\* proton affinities agree very well with the experimental values for isopropyl amine and guanidine.<sup>9</sup> For in-solution studies, the best result for the isonicotinic acid tautomerization was obtained by utilizing the IEF-PCM/B3LYP/6-31G\* geometry.<sup>19</sup> Considering the basis set effect, the B3LYP geometry optimization led to negligible changes in the geometry for the (CH<sub>3</sub>)<sub>3</sub>NH<sup>+</sup> cation in aqueous solution when the 6-31G\* and 6-311++G\*\* basis sets were applied.<sup>6</sup> On the basis of all of those above, the IEF-PCM/B3LYP/6-31G\* geometry optimization was chosen for the formaldoxime and nitrosomethane solutes in the present study.

**Table 1. B3LYP/6-31G\* Optimized CH<sub>2</sub>NOH Geometric Parameters and CHELPG Charges in the Gas Phase and in Solution<sup>a</sup>**

|                   | gas                         |                   | CH <sub>2</sub> Cl <sub>2</sub> | MeOH   | water  |
|-------------------|-----------------------------|-------------------|---------------------------------|--------|--------|
|                   | calc. <sup>b</sup>          | exp. <sup>c</sup> |                                 |        |        |
| C=N               | 1.2737 (1.268) <sup>d</sup> | 1.276             | 1.2745                          | 1.2747 | 1.2747 |
| N–O               | 1.4023 (1.402)              | 1.408             | 1.4035                          | 1.4037 | 1.4037 |
| O–H               | 0.9702 (0.964)              | 0.956             | 0.9716                          | 0.9718 | 0.9719 |
| C–H <sub>c</sub>  | 1.0909                      | 1.085             | 1.0916                          | 1.0917 | 1.0917 |
| C–H <sub>t</sub>  | 1.0856                      | 1.086             | 1.0863                          | 1.0865 | 1.0866 |
| CNO               | 111.15 (111.5)              | 110.2             | 111.33                          | 111.34 | 111.36 |
| NOH               | 102.38 (103.2)              | 102.7             | 102.86                          | 102.99 | 103.01 |
| H <sub>c</sub> CN | 123.09                      | 121.8             | 123.16                          | 123.15 | 123.14 |
| H <sub>t</sub> CN | 116.66                      | 115.5             | 116.76                          | 116.77 | 116.78 |
| Charges           |                             |                   |                                 |        |        |
| C                 | 0.149                       |                   | 0.161                           | 0.163  | 0.164  |
| N                 | −0.298                      |                   | −0.328                          | −0.334 | −0.335 |
| O                 | −0.361                      |                   | −0.385                          | −0.389 | −0.390 |
| (O)H              | 0.389                       |                   | 0.415                           | 0.419  | 0.420  |
| (C)H <sub>c</sub> | 0.073                       |                   | 0.080                           | 0.082  | 0.082  |
| (C)H <sub>t</sub> | 0.049                       |                   | 0.057                           | 0.058  | 0.059  |
| DM <sup>d</sup>   | 0.116                       |                   | 0.202                           | 0.221  | 0.224  |
| DM <sup>e</sup>   | 0.129                       |                   | 0.219                           | 0.238  | 0.242  |

<sup>a</sup> Distances in Å, angles in degree. Subscripts c and t for the hydrogen atoms indicate cis and trans position with reference to the oxygen atom.

<sup>b</sup> Values in parentheses calculated from B3LYP/6-311++G\*\* optimization (ref 43). <sup>c</sup> Reference 44. <sup>d</sup> Dipole moment in Debye, as calculated from CHELPG charges. <sup>e</sup> Dipole moment from DFT calculations.

**Gas-Phase Calculations.** Tables 1 and 2 show the B3LYP/6-31G\* optimized geometric parameters for the trans CH<sub>2</sub>NOH and CH<sub>3</sub>NO, respectively, in the gas phase. Values are provided up to five digits in order to compare them with the in-solution values and pointing out the only small deviations (see the discussion in the next section).

For the trans CH<sub>2</sub>NOH, the largest deviation from the experimental values in bond lengths and bond angles are 0.014 Å for the O–H bond and 1.3° for the H<sub>c</sub>CN angle. The corresponding deviations are generally larger as calculated by Long et al.<sup>43</sup> at the B3LYP/6-311++G\*\* level (values in parentheses). Thus except for the prediction of the O–H bond length (also overestimated with the larger basis set) the simple B3LYP/6-31G\* optimization provides a balanced set of geometric parameters near the experimental ones.

Calculated geometric parameters using the 6-31G\* and 6-311++G\*\* basis sets at the B3LYP level are compared for CH<sub>3</sub>NO in Table 2. Except the overestimation of the C–N bond length by 0.008 Å using the 6-31G\* set compared with 0.003 Å calculated with the 6-311++G\*\* basis set, all other parameters have been better predicted with the lower basis set if the experimental uncertainties are also considered. The B3LYP/6-31G\* geometry is favorable even in comparison with those obtained from optimizations at much higher theoretical levels (values in parentheses). Although some “best” parameters show better agreement with the experimental values than those from the B3LYP/6-31G\* calculations, the best values were obtained at different levels. None of the high level optimizations predicted CH<sub>3</sub>NO geometry, where all parameters were superior as compared with the B3LYP/6-31G\* values.

Table 2. B3LYP Optimized CH<sub>3</sub>NO Geometric Parameters and CHELPG Charges in the Gas Phase and in Solution<sup>a</sup>

|                   | gas                                  |            |                  | CH <sub>2</sub> Cl <sub>2</sub> | MeOH   | water  |
|-------------------|--------------------------------------|------------|------------------|---------------------------------|--------|--------|
|                   | 6-31G*                               | 6-311++G** | exp <sup>b</sup> | 6-31G*                          | 6-31G* | 6-31G* |
| C–N               | 1.4878 (1.493, 1.480) <sup>c,d</sup> | 1.4828     | 1.480(±0.002)    | 1.4791                          | 1.4785 | 1.4785 |
| N=O               | 1.2111 (1.210, 1.204)                | 1.2019     | 1.211(±0.002)    | 1.2143                          | 1.2147 | 1.2147 |
| C–H <sub>i</sub>  | 1.0940 (1.102, 1.094)                | 1.0922     | 1.094(±0.002)    | 1.0941                          | 1.0941 | 1.0941 |
| C–H <sub>o</sub>  | 1.0965 (1.104, 1.093)                | 1.0942     | 1.094(±0.002)    | 1.0974                          | 1.0976 | 1.0977 |
| CNO               | 113.17 (112.6, 113.2)                | 114.05     | 113.2(±0.3)      | 113.54                          | 113.66 | 113.65 |
| NCH <sub>i</sub>  | 111.54 (111.0, 111.1)                | 111.81     | 111.0(±0.2)      | 111.71                          | 111.68 | 111.60 |
| NCH <sub>o</sub>  | 106.96 (107.1, 107.4)                | 106.67     | 107.2(±0.2)      | 106.82                          | 106.79 | 106.69 |
| Charges           |                                      |            |                  |                                 |        |        |
| C                 | 0.467                                | 0.565      |                  | 0.488                           | 0.489  | 0.485  |
| N                 | −0.184                               | −0.203     |                  | −0.201                          | −0.204 | −0.203 |
| O                 | −0.118                               | −0.134     |                  | −0.145                          | −0.149 | −0.150 |
| H <sub>i</sub>    | −0.071                               | −0.086     |                  | −0.065                          | −0.064 | −0.062 |
| H <sub>o</sub>    | −0.049                               | −0.071     |                  | −0.038                          | −0.036 | −0.035 |
| DM <sup>e,f</sup> | 2.255                                | 2.445      |                  | 2.702                           | 2.773  | 2.786  |
| DM <sup>e,f</sup> | 2.358                                | 2.586      |                  | 2.813                           | 2.885  | 2.897  |

<sup>a</sup> Distances in Å, angles in degree. <sup>b</sup> Mean structure from ref 45. H<sub>i</sub> and H<sub>o</sub> are hydrogen atoms in and out of the CNO plane. Uncertainties in parentheses were provided for the deuterated molecule, CD<sub>3</sub>NO. <sup>c</sup> Best values from ref 46, selected from CCSD, CCSD(T), and 2-RDM calculations using the cc-pVDZ basis set. <sup>d</sup> Best values from ref 47, selected from MP2, CASSCF (8-6), CISD, and CCSD calculations, applying both the 6-31G\*\* and 6-311++G\*\* basis sets with each method. <sup>e,f</sup> Dipole moments as calculated from CHELPG charges and from DFT, respectively.

Table 3. Single-Point Free Energies of CH<sub>3</sub>NO Relative to CH<sub>2</sub>NOH in Solution<sup>a</sup>

|                         | CH <sub>2</sub> Cl <sub>2</sub> |                          |                          |                         | MeOH                    |                          |                         |                         |
|-------------------------|---------------------------------|--------------------------|--------------------------|-------------------------|-------------------------|--------------------------|-------------------------|-------------------------|
|                         | $\Delta E_{\text{int}}$         | $\Delta G_{\text{solv}}$ | $\Delta G_{\text{th}}$   | $\Delta G_{\text{tot}}$ | $\Delta E_{\text{int}}$ | $\Delta G_{\text{solv}}$ | $\Delta G_{\text{th}}$  | $\Delta G_{\text{tot}}$ |
| MP2/aug-cc-pvdz         | 12.42                           | 0.56                     | −0.92                    | 12.06                   | 12.44                   | 0.79                     | −0.92                   | 12.31                   |
| MP2/aug-cc-pvtz         | 13.41                           | 0.54                     |                          | 13.03                   | 13.43                   | 0.77                     |                         | 13.28                   |
| MP2 <sub>CBS</sub>      | 13.83                           | 0.54                     |                          | 13.45                   | 13.85                   | 0.77                     |                         | 13.70                   |
| QCISD(T)/aug-cc-pvdz    | 11.43                           | 0.56                     |                          | 11.07                   | 11.44                   | 0.79                     |                         | 11.31                   |
| QCISD(T) <sub>CBS</sub> | 12.84                           | 0.54                     |                          | 12.46                   | 12.85                   | 0.77                     |                         | 12.70                   |
| B3LYP/aug-cc-pvtz       | 13.87                           | 0.19                     |                          | 13.14                   | 13.91                   | 0.33                     |                         | 13.32                   |
| water                   |                                 |                          |                          |                         |                         |                          |                         |                         |
|                         | $\Delta E_{\text{int}}$         |                          | $\Delta G_{\text{solv}}$ |                         | $\Delta G_{\text{th}}$  |                          | $\Delta G_{\text{tot}}$ |                         |
| MP2/aug-cc-pvdz         | 12.44                           |                          | 0.73                     |                         | −0.90                   |                          | 12.27                   |                         |
| MP2/aug-cc-pvtz         | 13.43                           |                          | 0.71                     |                         |                         |                          | 13.24                   |                         |
| MP2 <sub>CBS</sub>      | 13.85                           |                          | 0.71                     |                         |                         |                          | 13.66                   |                         |
| QCISD(T)/aug-cc-pvdz    | 11.43                           |                          | 0.73                     |                         |                         |                          | 11.26                   |                         |
| QCISD(T) <sub>CBS</sub> | 12.84                           |                          | 0.71                     |                         |                         |                          | 12.65                   |                         |
| B3LYP/aug-cc-pvtz       | 13.92                           |                          | 0.24                     |                         |                         |                          | 13.26                   |                         |

<sup>a</sup> Energies in kcal/mol. Geometries were optimized at the B3LYP/6-31G\* level in the indicated solvents both for CH<sub>2</sub>NOH and CH<sub>3</sub>NO.  $\Delta G_{\text{solv}}$  for CBS calculations utilized the MP2/aug-cc-pvtz values.  $\Delta G_{\text{th}}$  from B3LYP/6-31G\* calculations.

**Continuum Solvent Simulations.** IEF-PCM/B3LYP/6-31G\* optimized structure parameters in dichloromethane, methanol, and water are summarized in Tables 1 and 2. The geometries change only slightly compared with that in the gas phase. The largest change of almost 0.01 Å was found for the C–N bond in CH<sub>3</sub>NO. Any other change is nearly negligible.

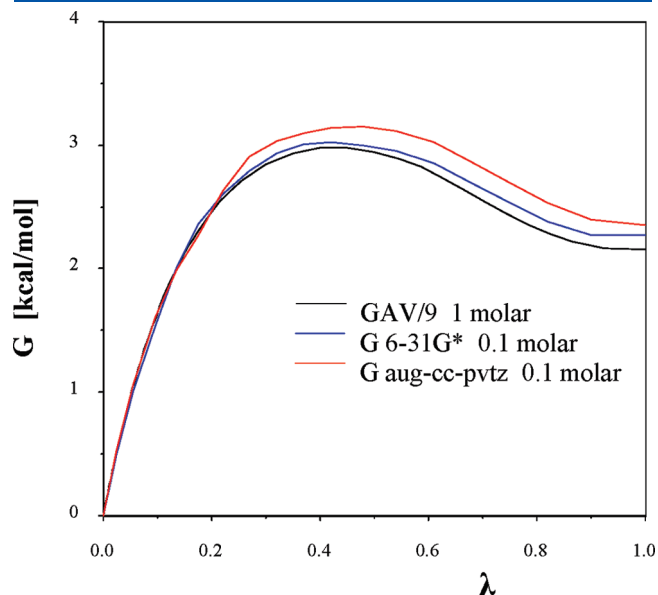
A surprising feature of the in-solution geometries is that the structural parameters are practically identical in methanol and water. This finding suggests that, despite the large difference in

the dielectric constants,  $\epsilon = 32.61$  vs 78.39, the polarization effect of the environment on the equilibrium geometry has reached a limit.

The B3LYP/6-31G\* dipole moment of CH<sub>2</sub>NOH increases by about 0.1 D upon solvation (Table 1.) The increase was calculated at about 0.5 D for CH<sub>3</sub>NO (Table 2). Indeed, the largest change in the C–N bond was recorded here. However, because the distance decreased instead of increasing, the larger dipole must have some different origin.



Tables 1 and 2 compare the ELPO fitted charges in the two phases. All net charges are larger in absolute value for  $\text{CH}_2\text{NOH}$  in solution than for the structure in the gas phase. The increased charges correspond to a larger charge separation, which is expected to increase the dipole moment. Since the negative charge domain is, however, embedded in the environment of positive atom charges, increase of the dipole moment remained still moderate for



**Figure 1.** Free energy perturbation curves for the single-solute  $\text{CH}_2\text{NOH}$  ( $\lambda = 0$ ) to  $\text{CH}_3\text{NO}$  ( $\lambda = 1$ ) transformation in water: (blue line) 6-31G\* charges and (red line) aug-cc-pvtz charges. The black line stands for the solvation free energy change for 1 mol solute in the molar solution model including nine moles of solutes in the box.

formaldoxime. In contrast, there is a flow of charges toward the NO group in  $\text{CH}_3\text{NO}$ . The sum of the NO charges is more negative by 0.04–0.05 units in solution than in the gas phase. Tables 1 and 2 compare the quantum-mechanical dipole moments with those calculated from the point-charge model. The deviations are 0.02–0.11 D units, an acceptable reproduction of the exact in-solution values.

The relative internal energies calculated at different theoretical levels for the tautomers are compared in Table 3. The effect of the different solvents is 0.05 kcal/mol at most. The theoretical level lets, however, the relative energies vary within a 2.5 kcal/mol energy range. The basis set effect at the MP2 level is 1.41 kcal/mol. The post-MP2 correction, (QCISD(T)/aug-cc-pvdz – MP2/aug-cc-pvdz) is –1.0 kcal/mol indicating remarkable correlation effect beyond the MP2 level. The B3LYP/aug-cc-pvtz relative internal energy is larger by 1.05 – 1.08 kcal/mol than the ab initio QCISD(T)<sub>CBS</sub> value.

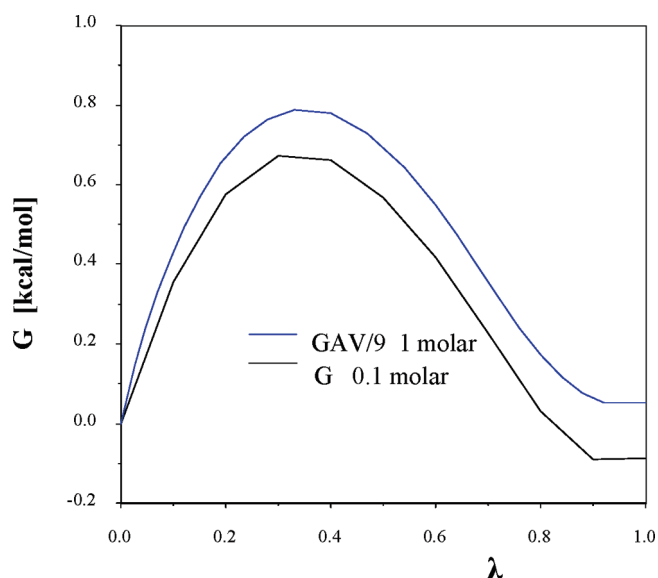
Relative solvation free energies are within the 0.2–0.8 kcal/mol range, thus they further decrease the stability of the nitrosomethane tautomer compared to the formaldoxime form. In total, the relative stability was calculated at about 11.1–13.7 kcal/mol, considering also thermal corrections. Long et al.<sup>43</sup> predicted 13.4–14.4 kcal/mol relative energy in water at the MP2/6-311++G\*\*+SCIPCM and B3LYP/6-311++G\*\*+SCIPCM levels, close to the present ones. Furthermore, they pointed out that consideration of two water molecules in hydrogen bonds to the solute would increase the energy separation by another 2–4 kcal/mol. Our approach for considering the explicit water molecules were performed through Monte Carlo simulations.

**Monte Carlo Simulations.** *0.11 M Model.* Two models with a single solute (1 mol) in a box corresponding to about 9 dm<sup>3</sup> have been studied without and with consideration of the Ewald summation, which accounts for the long-range electrostatic effects. Although the formal concentration is about 0.11 M, if no Ewald summation

**Table 4.** CHELPG Charges from Different Levels of Calculations<sup>a</sup>

|   | $\text{CH}_2\text{Cl}_2$ |                      |                    |                    | Water               |                      |                    |                    |
|---|--------------------------|----------------------|--------------------|--------------------|---------------------|----------------------|--------------------|--------------------|
|   | B3LYP<br>6-311++G**      | B3LYP<br>aug-cc pvtz | MP2<br>aug-cc pvdz | MP2<br>aug-cc pvtz | B3LYP<br>6-311++G** | B3LYP<br>aug-cc pvtz | MP2<br>aug-cc pvdz | MP2<br>aug-cc pvtz |
| <b><math>\text{CH}_2\text{NOH}</math></b> |                          |                      |                    |                    |                     |                      |                    |                    |
| C   | 0.241                    | 0.232                | 0.245              | 0.231              | 0.246               | 0.238                | 0.249              | 0.235              |
| N   | –0.363                   | –0.364               | –0.371             | –0.367             | –0.372              | –0.374               | –0.379             | –0.376             |
| O   | –0.421                   | –0.389               | –0.401             | –0.402             | –0.428              | –0.396               | –0.408             | –0.409             |
| H   | 0.430                    | 0.408                | 0.417              | 0.417              | 0.437               | 0.416                | 0.424              | 0.424              |
| H <sub>c</sub>                            | 0.078                    | 0.078                | 0.075              | 0.082              | 0.080               | 0.080                | 0.078              | 0.084              |
| H <sub>i</sub>                            | 0.035                    | 0.035                | 0.035              | 0.040              | 0.037               | 0.037                | 0.037              | 0.042              |
| DM <sup>b,c</sup>                         | 0.475                    | 0.485                | 0.511              | 0.528              | 0.510               | 0.518                | 0.539              | 0.557              |
| DM <sup>b,c</sup>                         | 0.521                    | 0.523                | 0.554              | 0.572              | 0.560               | 0.559                | 0.586              | 0.605              |
| <b><math>\text{CH}_3\text{NO}</math></b>  |                          |                      |                    |                    |                     |                      |                    |                    |
| C   | 0.588                    | 0.539                | 0.598              | 0.545              | 0.587               | 0.541                | 0.601              | 0.548              |
| N   | –0.221                   | –0.212               | –0.259             | –0.251             | –0.223              | –0.215               | –0.264             | –0.256             |
| O   | –0.171                   | –0.161               | –0.113             | –0.112             | –0.178              | –0.167               | –0.116             | –0.116             |
| H <sub>i</sub>                            | –0.078                   | –0.070               | –0.093             | –0.077             | –0.075              | –0.068               | –0.091             | –0.075             |
| H <sub>o</sub>                            | –0.059                   | –0.048               | 0.067              | –0.053             | –0.056              | –0.045               | –0.065             | –0.050             |
| DM <sup>b,c</sup>                         | 3.012                    | 2.895                | 2.608              | 2.622              | 3.116               | 3.002                | 2.696              | 2.711              |
| DM <sup>b,c</sup>                         | 3.172                    | 3.051                | 2.779              | 2.790              | 3.280               | 3.162                | 2.871              | 2.883              |

<sup>a</sup> Geometries from B3LYP/6-31G\* optimizations in the corresponding solvent. <sup>b,c</sup> See the footnote for Table 1.



**Figure 2.** Free energy perturbation curves for the (black line) single-solute  $\text{CH}_2\text{NOH}$  ( $\lambda = 0$ ) to  $\text{CH}_3\text{NO}$  ( $\lambda = 1$ ) transformation in dichloromethane, aug-cc-pvtz charges, and (blue line) the solvation free energy change for 1 mol solute in the molar solution model including nine moles of solutes in the box.

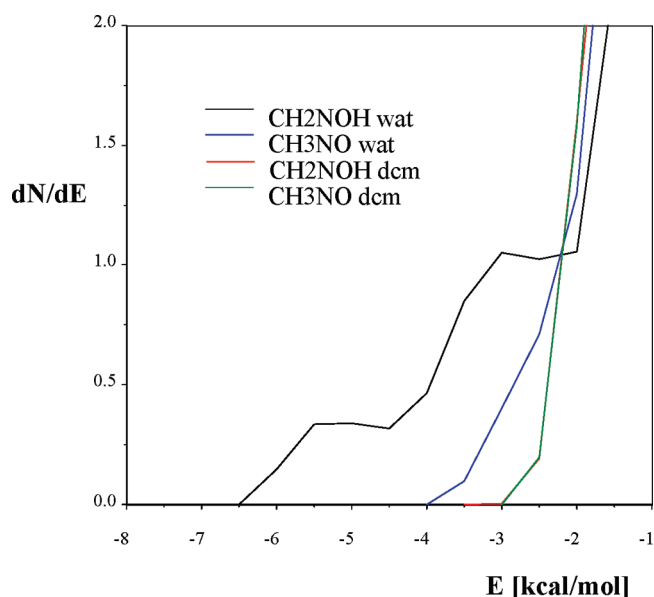
**Table 5. Relative Solvation Free Energy from Monte Carlo Simulations<sup>a</sup>**

|                     | $\text{CH}_2\text{Cl}_2$ | water            |
|---------------------|--------------------------|------------------|
| single-solute       |                          |                  |
| infinitely dilute   |                          |                  |
| B3LYP/aug-cc-pvtz   | $-0.46 \pm 0.03$         | $1.71 \pm 0.06$  |
| Ewald               |                          |                  |
| B3LYP/6-31G*        |                          | $2.27 \pm 0.05$  |
| B3LYP/aug-cc-pvtz   | $-0.09 \pm 0.03$         | $2.36 \pm 0.06$  |
| nine-solutes, Ewald |                          |                  |
| B3LYP/aug-cc-pvtz   | $0.47 \pm 0.05$          | $19.38 \pm 0.11$ |
| per one solute      | $0.05 \pm 0.01$          | $2.15 \pm 0.01$  |

<sup>a</sup> Solute charges derived from B3LYP calculations with 6-31G\* and aug-cc-pvtz basis sets.

is applied the model accounts for the change of the solvation free energy for the tautomers only in an infinitely dilute solution (Table 5).

Figure 1 shows the FEP curves for calculating the relative solvation free energy for the  $\text{CH}_2\text{NOH}$  to  $\text{CH}_3\text{NO}$  transformation in aqueous solution when Ewald summation was considered. The concentration corresponded to about  $0.11 \text{ mol/dm}^3$  through the simulations. The curves run fairly similarly applying either the B3LYP/6-31G\* or the B3LYP/aug-cc-pvtz charge set for the solutes. The relative solvation free energies of  $2.27 \pm 0.05$  and  $2.36 \pm 0.06 \text{ kcal/mol}$ , respectively, do not differ significantly (Table 5) despite the remarkably different C and N atom charges (Tables 1, 2, and 4). Thus, the solvation stabilizes the  $\text{CH}_2\text{NOH}$  form by about  $2.3 \text{ kcal/mol}$  in aqueous solution. In contrast, Figure 2 shows that the in-DCM FEP curve predicts stabilization of the  $\text{CH}_3\text{NO}$  form upon solvation by  $0.09 \text{ kcal/mol}$  in spite of the very similar B3LYP/aug-cc-pvtz atomic charges for the solutes in DCM and water. The signs were preserved when the FEP



**Figure 3.**  $\text{CH}_2\text{NOH}$ –solvent and  $\text{CH}_3\text{NO}$ –solvent pair-energy distribution functions using the aug-cc-pvtz charge sets. Pedfs for (black line)  $\text{CH}_2\text{NOH}$  and (blue line)  $\text{CH}_3\text{NO}$  in water. Integral values and integration limits ( $E$  in kcal/mol) in parentheses for  $\text{CH}_2\text{NOH}$  in water:  $0.57$  ( $-4.5$ ) and  $2.27$  ( $-2.5$ ). Pedfs for (red line)  $\text{CH}_2\text{NOH}$  and (green line)  $\text{CH}_3\text{NO}$  in dichloromethane.

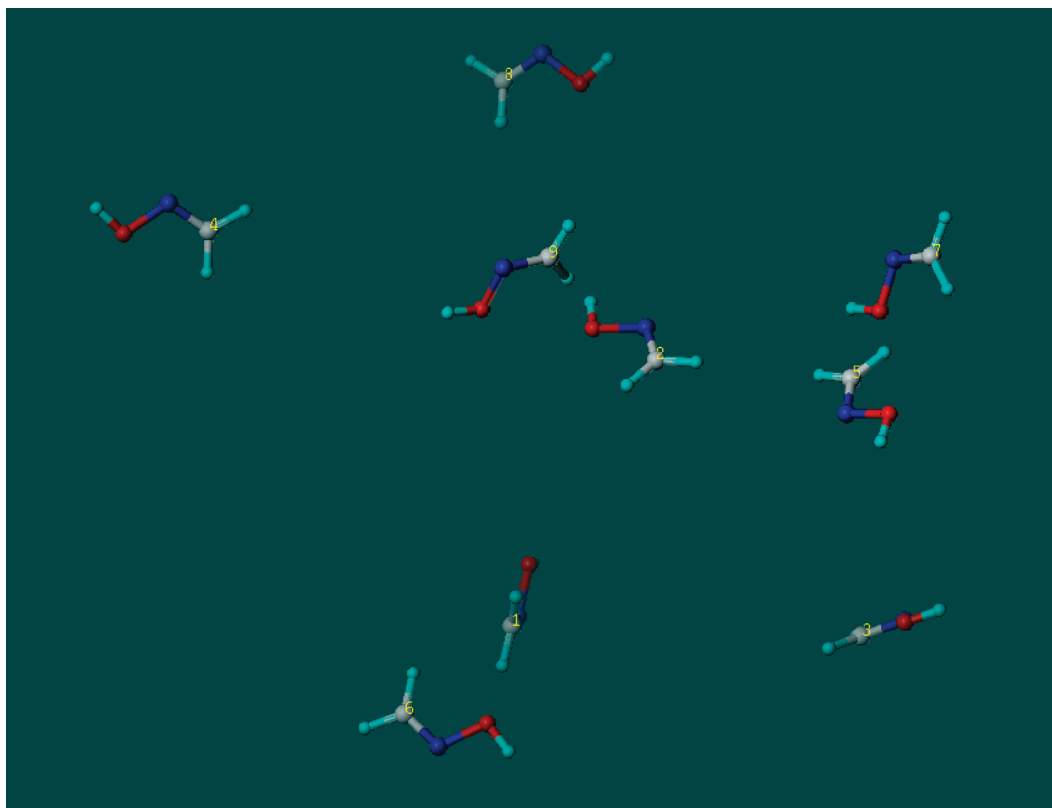
**Table 6. Coordination Numbers for a Single Solute in Aqueous Solution<sup>a</sup>**

| charges               | 6-31G*                   | aug-cc-pvtz              |
|-----------------------|--------------------------|--------------------------|
|                       | $\text{CH}_2\text{NOH}$  |                          |
| (O)H...O <sub>w</sub> | 1.14 (2.50)              | 1.14 (2.45)              |
| O...H <sub>w</sub>    | 1.00 (2.50)              | 0.97 (2.45)              |
| N...H <sub>w</sub>    | 0.32 (2.60)              | 0.43 (2.60)              |
|                       | $\text{CH}_3\text{NO}$   |                          |
| O...H <sub>w</sub>    | 0.63 (2.35) <sup>b</sup> | 0.55 (2.25) <sup>b</sup> |
| N...H <sub>w</sub>    | 0.21 (2.50) <sup>b</sup> | 0.18 (2.50) <sup>b</sup> |

<sup>a</sup> Charges from the CHELPG fit of the IEF-PCM/B3LYP molecular electrostatic potential calculated with the indicated basis set. Values in parentheses stand for the boundary of the first solvation shell from the corresponding radial distribution function. <sup>b</sup> End of a shoulder.

calculations were applied for the infinitely dilute model (Table 5), but the relative free energies were more negative/less positive by  $0.4$ – $0.7 \text{ kcal/mol}$  in this case compared with models considering the Ewald summation.

Two conclusions have been drawn on the basis of the indicated curves in Figures 1 and 2. Use of the 6-31G\* or aug-cc-pvtz charges for calculating the relative solvation free energy has a minor effect on the results even in the case of the very polar water solvent with good capacity for hydrogen bond formation to the solute. Instead, the physical-chemical character of the solvent has the largest effect on the calculated  $\Delta G_{\text{solv}}/\text{MC}$ . The dipole moment of the dichloromethane solvent molecules is  $2.38 \text{ D}$  in the OPLS parametrization as compared to  $2.17 \text{ D}$  for the TIP4P water. The FEP results have been interpreted so that the stabilization of the formaldoxime form in water is related to the predominance of the hydrogen bond formation to the OH group, because the NO group



**Figure 4.** Last snapshot for the molar  $\text{CH}_2\text{NOH}$  solution with water solvent. Short  $\text{C} \cdots \text{C}$  distances: 4.14 Å ( $\text{C}_5 \cdots \text{C}_7$ ) and 4.16 Å ( $\text{C}_2 \cdots \text{C}_9$ ). By considering the PBC,  $R(\text{C}_4 \cdots \text{C}_5) = 5.32$  Å.

is only a weak hydrogen bond acceptor. Through the  $\text{CH}_2\text{NOH}$  to  $\text{CH}_3\text{NO}$  transformation the dipole moment considerably increases. Since solute–solvent hydrogen bond cannot be formed in the dichloromethane solvent, the dipole–dipole interactions become dominant slightly favoring the nitrosomethane tautomer.

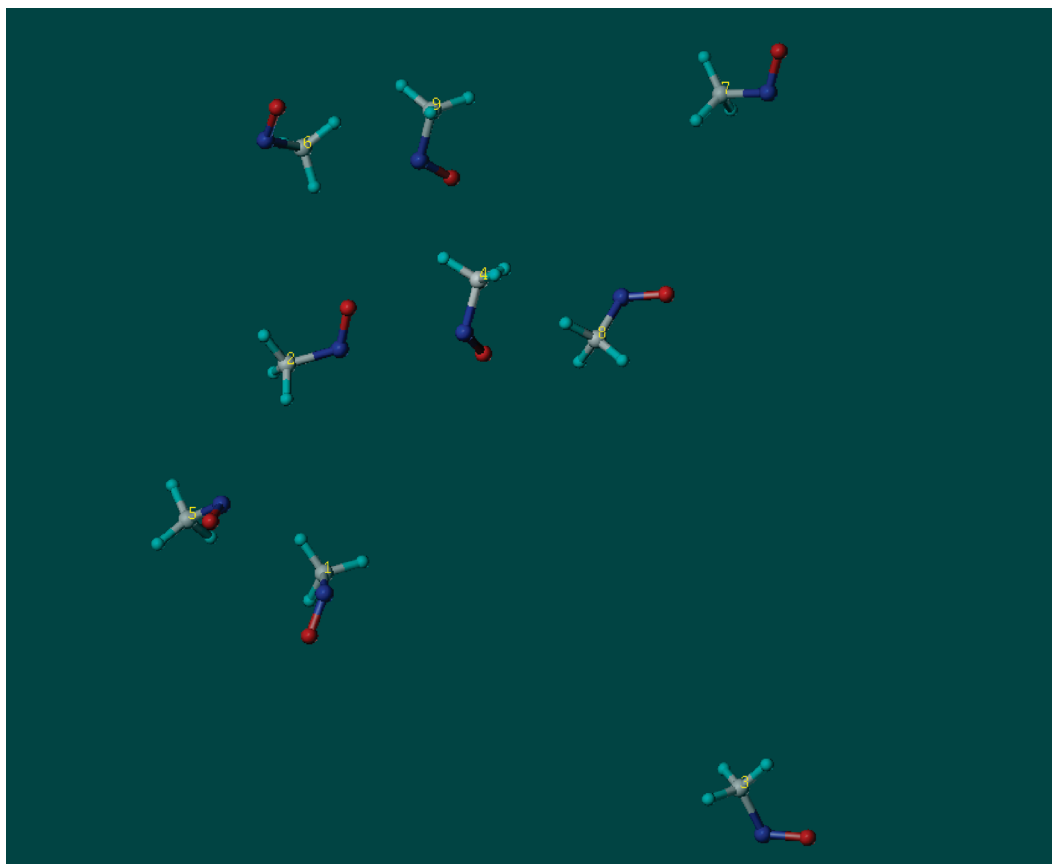
The solute–solvent pair-energy distribution functions (pedf) are shown in Figure 3. Integration of these functions up to their first minima or until an inflection point on a plateau has been interpreted as the number of the strongly bound solute molecules in hydrogen bonds to the solute.<sup>3–5,27–29,31,39,41,42,48</sup> The sum of the coordination numbers for a solute in the Table 6 defines an upper limit for the solute–solvent hydrogen bonds. Accordingly, about 2.5 and 0.7–0.8 hydrogen bonds are allowed to  $\text{CH}_2\text{NOH}$  and to  $\text{CH}_3\text{NO}$ , respectively, in aqueous solution. The footnote of Figure 3 indicates 2.3 hydrogen bonds to  $\text{CH}_2\text{NOH}$  in water. This number is reasonably smaller than the sum of the corresponding coordination numbers. The curve indicates a resolved and an unresolved peak suggesting stronger and weaker hydrogen bonds to the solute. Information from pedfs are not enough, however, to find the individual numbers of the (O)H $\cdots$ O(solvent), O..H(solvent), and N..H(solvent) hydrogen bonds contributing to the total calculated from the integration of pedf up to  $E = -2.5$  kcal/mol. The pedf in DCM has no minimum–maximum structure, in accord with the lack of solute–solvent hydrogen bonds.

No local minimum for any pedf has been observed for  $\text{CH}_3\text{NO}$ . Indeed, the sum of the coordination numbers in Table 6 remains below 1 in aqueous solution, suggesting that not even one stable hydrogen bond of any type is expected to be formed to this solute. The TIP4P hydrogens must be loosely localized around the

O and N atoms, and the pedf monotonically increases without indicating special interactions. The lack of a maximum for the DCM pedf suggests that the solute–solvent dipole–dipole interaction is not strong enough for stably localizing a solvent molecule around the solute. The energy effect of all, close and more remote solvents, is enough, however, for an overall, small, solvation-related stabilization of the nitrosomethane form in DCM.

**Molar Solution Models.** Deviations of the calculated relative solvation free energies,  $\Delta G_{\text{solv}}/\text{MC}$  obtained for the  $\text{CH}_2\text{NOH}$  to  $\text{CH}_3\text{NO}$  transformation considering the 0.11 and 1 M models are about 0.21 kcal/mol in aqueous solution and 0.14 kcal/mol in dichloromethane (Table 5). In the latter case, even the sign has changed. The results are on the verge of the 99% significance corresponding to 3 SD. Before a further analysis, however, the reliability of the results should be studied. In this respect, it is not a matter of consideration in the present study whether the results agree well with (otherwise nonavailable) experimental data. Our main goal in this paper is the comparison of the calculated  $\Delta G_{\text{solv}}/\text{MC}$  for the  $\text{CH}_2\text{NOH}$  to  $\text{CH}_3\text{NO}$  transformation in case of 0.11 and 1 M models using equal OPLS-AA parameters and pointing out the possible difference of the  $\Delta G_{\text{solv}}/\text{MC}$  values at different solute concentrations.

The dG increments, averaged over 7.5 M configurations following 7.5 M configurations considered in the equilibration phase, are probably reliable values for small, neutral organic molecules. An SD value up to about 0.1 kcal/mol is in accord with those in former studies, where comparisons with experimental values were possible.<sup>19,48</sup> The SDs of  $\Delta G_{\text{solv}}/\text{MC}$  values for the molar models are similar, so the results in this respect seem to be acceptable. The question is, however, whether the solution structure does represent a momentary state of an equilibrium ensemble, and



**Figure 5.** Last snapshot for the molar  $\text{CH}_3\text{NO}$  solution with water solvent. Short  $\text{C}\cdots\text{C}$  distances: 3.62 Å ( $\text{C}_6\cdots\text{C}_9$ ) and 3.96 Å ( $\text{C}_1\cdots\text{C}_5$ ). By considering the PBC,  $R(\text{C}_3\cdots\text{C}_7) = 5.77$  Å.

the energies/free energies for the given state are favorably comparable with the ensemble averages.

The problem is primarily related to the molar model. In the 0.11 molar model, only the solvent molecules have to arrange around the single solute in an equilibrated fashion under the influence of solvent molecules in the replica boxes. Possible solute association and concomitant solvent reorganization is, however, the central problem in considering solution models with more than a single solute.

As mentioned in the Introduction, non-negligible solute association was observed in about molar solutions of several small, organic species. Figures 4–7 show the last snapshot of the 75 M configurations for both solutes in both solvents. Two to three  $\text{C}\cdots\text{C}$  distances were shorter than 5 Å, which means that 3–4 molecules must be involved in such close contacts.<sup>4,5</sup> Footnotes for the figures specify the molecules forming the short distances in the present simulation.

Since the snapshots are the last ones of the corresponding simulations, the question may be raised whether the structures are peculiar and the short distances come into existence only by the end of the 75 M long simulations. Then the systems may not be well equilibrated.

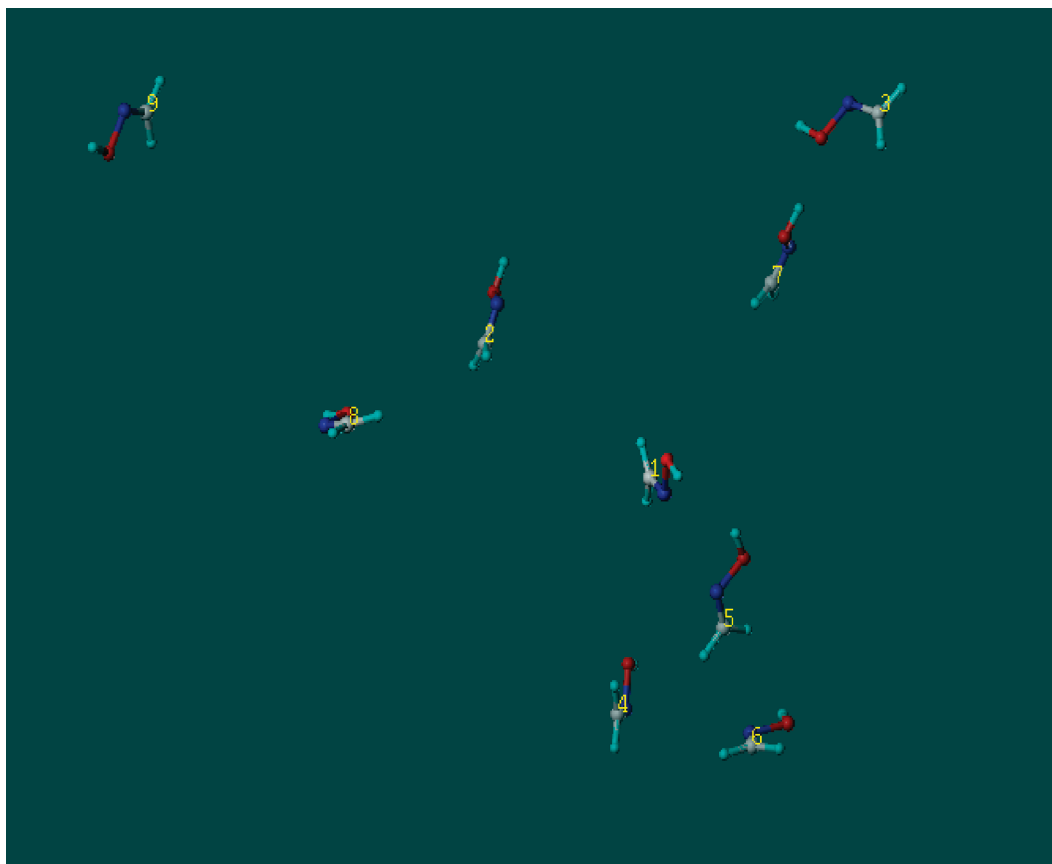
Table 7 shows the statistical result for the distribution of the 36  $\text{C}\cdots\text{C}$  distances in five considered snapshots. The first snapshot for any system was taken at configuration serial number 37.5 or 45 M, and the separation of the configurations were at least 7.5 M for the further snapshots. One-three short distances ( $R(\text{C}\cdots\text{C}) < 5$  Å) appeared in earlier snapshots, as well, starting at latest in configuration 52.5 M with the exception of the  $\text{CH}_3\text{NO}$  solute in

DCM. The relatively small SD suggests that there was no consistent shift of the  $\text{C}\cdots\text{C}$  distances resulting in 2–3 short distances at configuration 75 M. The mean values show most  $\text{C}\cdots\text{C}$  distances in the 11–13 Å range in aqueous solution, whereas larger solute separations are more favored in DCM.  $R(\text{C}\cdots\text{C}) = 11\text{--}13$  Å for the reference atoms is in accord with the value of 11.84 Å for the shortest separation in case of a uniform local density in any molar solution by considering an “own-volume” cube for the solute.<sup>5,6</sup> The important finding is, however, that 15–25% of the  $\text{C}\cdots\text{C}$  distances are shorter than 9 Å. This must indicate a non-negligible solute association.

The solute–solute,  $E_{\text{XX}}$ , and solute–solvent,  $E_{\text{SX}}$  interaction energies (considering the minimum image convention if necessary) change only slightly. It is to be emphasized that the values in Table 7 do not refer to the considered snapshots but each  $E_{\text{XX}}$  and  $E_{\text{SX}}$  value is the average over 7.5 M configurations with the last of them indicated as 37.5 M, 45 M, ..., 75 M. None of the series of data shows systematic increase or decrease, all of them slightly oscillate about the corresponding average value. Considering also the small standard deviations for the relative solvation free energy increments, structural and energetic averages over the last 30 M configurations have been accepted, and the simulations were considered as converged.

Then the change in the relative solvation free energy for  $\text{CH}_3\text{NO}$  with respect to  $\text{CH}_2\text{NOH}$  may be evaluated with confidence. The ultimate result is that  $\Delta G_{\text{solv}}/\text{MC} = \Delta\mu^0(\text{solv})$  for the molar solution differs by up to 0.2 kcal/mol from the  $\Delta G_{\text{solv}}/\text{MC}$  value for the 0.11 molar solution. The small difference suggests, as the most important conclusion, that the non-negligible solute





**Figure 6.** Last snapshot for the molar  $\text{CH}_2\text{NOH}$  solution with dichloromethane solvent. Short  $\text{C}\cdots\text{C}$  distances: 3.70 Å ( $\text{C}_5\cdots\text{C}_6$ ), 4.44 Å ( $\text{C}_4\cdots\text{C}_5$ ), and 4.67 Å ( $\text{C}_4\cdots\text{C}_6$ ). By considering the PBC,  $R(\text{C}_3\cdots\text{C}_9) = 8.27$  Å.

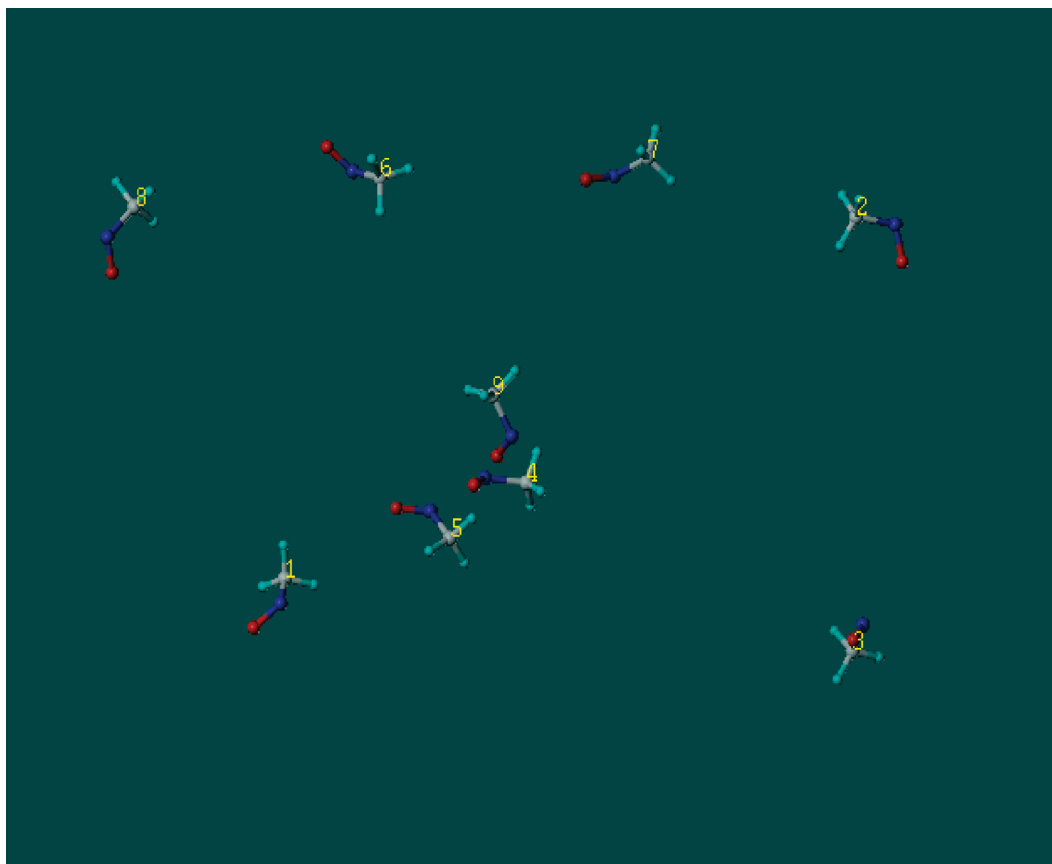
association for the studied molar systems does not lead to large deviation in  $\Delta G_{\text{solv}}/\text{MC}$  when this value is compared with that for a 9–10 times more dilute solution.

**Prediction of the Relative Activity Coefficients.** The 0.14–0.21 kcal/mol solvation free energy differences calculated above by the FEP procedure must be subject to uncertainties due to charge parametrization, considered cutoffs, double-wide sampling, etc. Nonetheless, if the results are accepted as significant then the following argument applies.

From eq 6b, the  $RT \ln[(\gamma_n c_n)_B/(\gamma_m c_m)_A]$  term is responsible for the calculated difference. The concentrations were stably about 0.11 molar for both solutions with a single  $\text{CH}_3\text{NO}$  and  $\text{CH}_2\text{NOH}$  solute, thus the difference up to 0.21 kcal/mol comes from the  $RT \ln \gamma_{(\text{CH}_3\text{NO})}/\gamma_{(\text{CH}_2\text{NOH})}$  term. With 0.21 kcal/mol for the aqueous solution,  $\gamma_{(\text{CH}_3\text{NO})}/\gamma_{(\text{CH}_2\text{NOH})}$  is 1.4. In dichloromethane, the difference of −0.14 kcal/mol predicting a  $\gamma_{(\text{CH}_3\text{NO})}/(\gamma_{(\text{CH}_2\text{NOH})})$  ratio of 0.8. It is to be emphasized that the present theoretical method allows only calculation of the relative solvation contribution to the standard chemical potential and accordingly only relative values for the activity coefficients can be predicted. The 20–40% deviations for the  $\gamma$  values do not seem to be unreasonably large. It is interesting that the relative values change from 1.4 to 0.8 when the solvent is dichloromethane instead of water. The largely different capacity for hydrogen-bond formation of the two solvents, the remarkably different dipole moments of the tautomers may explain the changes in the relative  $\gamma$  values, but no clear relationship between the solution structure in a given solvent and the solvation terms has been found.

The above relative  $\gamma$  values refer, however, to a hypothetical chemical situation, when only one or the other unique structure of the tautomers can be present in the solution. Although this may be possible if a very large activation free energy prevents the equilibration, in case of a mobile equilibrium both tautomers must be present at a time. Thus 0.11 M systems with single tautomeric forms should be considered as representing only hypothetical solutions and related relative  $\gamma$  values. However, derivation of  $\Delta\mu^0(\text{solv})$  by means of the solvation free energy change for one molar solutions does not suffer from this problem even considering hypothetical states with unique tautomers because  $\gamma$ 's for both systems are equal to 1 by definition in this case. Use of the  $\Delta G_{\text{solv}}/\text{MC}$  for predicting  $\Delta\mu^0(\text{solv})$  by transformation of the solutes in molar solutions is always possible. Theoretical determination of this term for the estimation of  $K_c$  is especially useful in cases of dissociated salts, where no individual  $\gamma$  can be measured for the participating ions even at experimentally determined  $c_n/c_m$  ratios.<sup>1,9,49</sup>

Physically relevant products of relative  $\gamma$  values can be determined, however, in nonstandard states at different solute concentrations. For keto/enol tautomers, the ratio of the equilibrium concentrations were determined at different total solute concentrations by Moriyasu et al.<sup>49</sup> Let  $c_{B2}/c_{A2}$  be larger than  $c_{B1}/c_{A1}$  and  $n_A + n_B = N_{\text{tot}}$  tautomeric molecules ( $n_B > n_A$ ) be dissolved in some  $V$  volume corresponding to  $N_{\text{tot}}/V = c_{\text{tot}} = c_A + c_B$ . For the FEP process, two solvent boxes have to be created with  $(n_{A1} + n_{B1})$  and  $(n_{A2} + n_{B2})$  tautomeric solute molecules in volumes  $V_1$  and  $V_2$  providing  $(c_{A1} + c_{B1})$  and  $(c_{A2} + c_{B2})$ , respectively. The solvation



**Figure 7.** Last snapshot for the molar  $\text{CH}_3\text{NO}$  solution with dichloromethane solvent. Short  $\text{C} \cdots \text{C}$  distances: 3.92 Å ( $\text{C}_4 \cdots \text{C}_9$ ), 4.07 Å ( $\text{C}_4 \cdots \text{C}_5$ ), 4.78 Å ( $\text{C}_5 \cdots \text{C}_9$ ), and 6.55 Å ( $\text{C}_1 \cdots \text{C}_5$ ).

parts of the Gibbs functions for the solutes in the corresponding solutions are (using shortened symbols for  $\mu(\text{solv})$  in eq 1b)

$$G_1(\text{solv}) = n_{A1}(\mu_A^0(\text{solv}) + RT \ln \gamma_{A1} c_{A1}) + n_{B1}(\mu_B^0(\text{solv}) + RT \ln \gamma_{B1} c_{B1}) \quad (8a)$$

$$G_2(\text{solv}) = n_{A2}(\mu_A^0(\text{solv}) + RT \ln \gamma_{A2} c_{A2}) + n_{B2}(\mu_B^0(\text{solv}) + RT \ln \gamma_{B2} c_{B2}) \quad (8b)$$

By a suitable choice for  $n_A$  and  $n_B$ , one can ensure that  $c_{A1} = n_A/V_1$ ,  $c_{B1} = n_B/V_1$ ,  $c_{A2} = (n_A - w)/V_2$ ,  $c_{B2} = (n_B + w)/V_2$  and  $K_c = (\gamma_{B2}/\gamma_{A2})(c_{B2}/c_{A2}) = (\gamma_{B1}/\gamma_{A1})(c_{B1}/c_{A1})$ . This means that  $n_{B1} = n_B$ ,  $n_{A1} = n_A$ , and “ $w$ ” A solute molecules should be transformed to B in box 2 resulting in  $n_{A2} = (n_A - w)$  and  $n_{B2} = (n_B + w)$ . Then the change of the  $G(\text{solv})$  functions is

$$\Delta G(\text{solv}) = w[\mu_B^0(\text{solv}) - \mu_A^0(\text{solv}) + RT \ln(\gamma_{B2}/\gamma_{A2})(c_{B2}/c_{A2})] + n_B RT \ln(\gamma_{B2}/\gamma_{B1})(c_{B2}/c_{B1}) - n_A RT \ln(\gamma_{A1}/\gamma_{A2})(c_{A1}/c_{A2}) \quad (9a)$$

By adding  $w\Delta\mu^0(\text{int})$  to both sides of eq 9a, the term proportional to “ $w$ ” on the right side will be zero because  $\Delta\mu^0(\text{int}) + \Delta\mu^0(\text{solv}) = -RT \ln K_c$  is the opposite of the third term in brackets expressing  $K_c$  with equilibrium concentrations and activity constants at

$c_{B2}/c_{A2}$ . Accordingly

$$\begin{aligned} \Delta G(\text{solv}) + w\Delta\mu^0(\text{int}) &= n_B RT \ln(\gamma_{B2}/\gamma_{B1})(c_{B2}/c_{B1}) - n_A RT \ln(\gamma_{A1}/\gamma_{A2})(c_{A1}/c_{A2}) \\ &= n_B RT \ln(\gamma_{B2}/\gamma_{A2})(\gamma_{A1}/\gamma_{B1})(c_{B2}/c_{B1})(c_{A1}/c_{A2}) \\ &\quad - (n_A + n_B) RT \ln(\gamma_{A1}/\gamma_{A2})(c_{A1}/c_{A2}) \end{aligned} \quad (9b)$$

In eq 9b the concentrations are known (preset), so denoting them as  $f(c)$ , eq 9c follows.

$$\begin{aligned} (\Delta G(\text{solv}) + w\Delta\mu^0(\text{int}) - f(c)) &= n_B RT \ln(\gamma_{B2}/\gamma_{A2})(\gamma_{A1}/\gamma_{B1}) - N_{\text{tot}} RT \ln(\gamma_{A1}/\gamma_{A2}) \end{aligned} \quad (9c)$$

The second logarithmic term in eq 9c is about zero because two activity coefficients for the same solute must be close to each other in dilute solutions with a ratio of about 1. For 1 mol of the solute, an approximate expression could be then derived as

$$\begin{aligned} [\Delta G(\text{solv}) + w\Delta\mu^0(\text{int}) - f(c)]/N_{\text{tot}} &\approx (n_B/N_{\text{tot}}) RT \ln(\gamma_{B2}/\gamma_{A2})(\gamma_{A1}/\gamma_{B1}) \end{aligned} \quad (9d)$$

From eq 9d, the  $(\gamma_{B2}/\gamma_{A2})/(\gamma_{B1}/\gamma_{A1})$  ratio can be estimated; thus, the convergence of the  $\gamma_B/\gamma_A$  ratio upon dilution (solution 2 is more dilute than solution 1) can be followed. If the limit value of  $c_{B2}/c_{A2}$  for a dilute solution is known from

**Table 7.** Solute–Solute and Solute–Solvent Interaction Energies and the Calculated Distribution of the C–C Distances in the Molar Solutions<sup>a</sup>

|                          | 37.5 M    | 45 M      | 52.5 M    | 60 M      | 67.5 M    | 75 M      |           |
|--------------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| water                    |           |           |           |           |           |           |           |
| CH <sub>2</sub> NOH      |           |           |           |           |           |           |           |
| <i>E</i> <sub>XX</sub>   | −2.1      | −2.7      | −2.5      | −2.9      | −2.9      | −1.9      |           |
| <i>E</i> <sub>SX</sub>   | −142.4    | −138.7    | −140.2    | −136.6    | −140.2    | −138.6    |           |
| CH <sub>3</sub> NO       |           |           |           |           |           |           |           |
| <i>E</i> <sub>XX</sub>   | −2.2      | −3.0      | −4.4      | −4.1      | −4.7      | −3.9      |           |
| <i>E</i> <sub>SX</sub>   | −96.8     | −94.3     | −93.6     | −93.3     | −91.4     | −96.1     |           |
| dichloromethane          |           |           |           |           |           |           |           |
| CH <sub>2</sub> NOH      |           |           |           |           |           |           |           |
| <i>E</i> <sub>XX</sub>   | −2.3      | −7.1      | −6.9      | −8.2      | −5.5      | −4.6      |           |
| <i>E</i> <sub>SX</sub>   | −92.2     | −86.7     | −87.1     | −86.7     | −88.7     | −88.7     |           |
| CH <sub>3</sub> NO       |           |           |           |           |           |           |           |
| <i>E</i> <sub>XX</sub>   | −3.0      | −2.2      | −1.6      | −2.0      | −2.0      | −1.9      |           |
| <i>E</i> <sub>SX</sub>   | −89.4     | −91.1     | −91.7     | −91.6     | −91.5     | −91.7     |           |
| C . . . C distances in Å |           |           |           |           |           |           |           |
|                          | <5        | 5–7       | 7–9       | 9–11      | 11–13     | 13–15     | >15       |
| water                    |           |           |           |           |           |           |           |
| CH <sub>2</sub> NOH      | 1.8 ± 0.6 | 2.0 ± 0.8 | 3.2 ± 0.9 | 5.2 ± 0.6 | 9.4 ± 1.0 | 7.6 ± 1.0 | 6.8 ± 0.5 |
| CH <sub>3</sub> NO       | 1.4 ± 0.4 | 3.6 ± 0.5 | 3.8 ± 0.7 | 6.6 ± 0.4 | 9.4 ± 0.9 | 6.8 ± 1.1 | 4.4 ± 0.8 |
| dichloromethane          |           |           |           |           |           |           |           |
| CH <sub>2</sub> NOH      | 1.0 ± 0.6 | 4.6 ± 1.0 | 3.4 ± 0.5 | 5.2 ± 0.5 | 6.4 ± 0.6 | 6.4 ± 0.8 | 9.0 ± 1.1 |
| CH <sub>3</sub> NO       | 0.6 ± 0.6 | 1.2 ± 0.2 | 4.2 ± 0.5 | 5.0 ± 1.2 | 8.6 ± 0.9 | 8.2 ± 1.1 | 8.2 ± 1.1 |

<sup>a</sup> *E*<sub>XX</sub> and *E*<sub>SX</sub> stand for the solute–solute and solute–solvent interaction energies, respectively, averaged over 7.5 M configurations and ending with configuration serial number of 37.5 M, ..., 75 M. Energies in kcal/mol. Standard deviations are about 0.1, and less than 1 kcal/mol for *E*<sub>XX</sub> and *E*<sub>SX</sub>, respectively in water.

experiment,  $K_c/(c_{B2}/c_{A2})_{\text{lim}}$  provides an estimate for the limit value of  $(\gamma_B/\gamma_A)$ .

Through the FEP process, “w” A molecules have to be transformed into B if  $c_{B2}/c_{A2} > c_{B1}/c_{A1}$ . At the same time  $V_1$  is to be modified to  $V_2$ . It could be a very time-consuming process if the two volumes differ considerably. The FEP process would need annihilation/development of a large number of solvent molecules in such a case. Furthermore, the indicated single-w calculations, although they are theoretically possible, require consideration of large boxes and correspondingly large numbers of solute molecules in order to ensure a smooth change of the concentrations if the a number of solute molecules to be transformed are not so simple integers as in the above example. Indeed, it would be much simpler keeping up the total volume and annihilating/transforming solute molecules in order to reach the requested ratio for the solute tautomers. The derivation of eq 9a is based on, however, the application of a single “w” value, but this requirement cannot be assured in cases when both some A and B molecules have to be annihilated. For example, using  $n_{B1} = 14$ ,  $n_{A1} = 6$ ,  $N_{\text{tot}} = 20$  in a model of 100 dm<sup>3</sup> solution, the  $n_B/n_A$  ratio is 7/3 and the concentrations are  $c_B = 0.14$  and  $c_A = 0.06$  in a 0.2 molar solution. If the  $n_B/n_A$  ratio is 8/2 in a 0.1 molar solution, then  $c_B = 0.08$  and  $c_A = 0.02$  should be reached by applying a single “w” and having 8 “B” and 2 “A” tautomeric species in the  $V_2 = 100$  dm<sup>3</sup> model solution box. Starting from the 0.2 molar box, 4 A and 6 B solutes should be annihilated, but it means that  $w_A = 4$  and  $w_B = -6$  in order to have  $n_{A2} = 2$  and  $n_{B2} = 8$ .

## CONCLUSIONS

A method has been proposed for calculating relative standard chemical potentials for solutes on a pure theoretical basis. The relative internal free energy for tautomers/conformers could be obtained by using ab initio/DFT methods for geometry optimization and free energy calculations. Applying the FEP method for the transformation of involved species, the solvation contribution to the relative standard chemical potential can be determined by considering one molar solution models. Comparison of the  $\Delta G_{\text{solv}}/\text{MC}$  value calculated for the one molar solution with those obtained for the system at other concentrations helps explore the ratio of the activity coefficients in nonstandard states. The method was applied in the present study to the tautomeric pair of formaldoxime and nitrosomethane with large structural differences. It was pointed out that  $\Delta G_{\text{solv}}/\text{MC}$  differs by up to 0.2 kcal/mol for the 1 and 0.11 M solutions, when atomic charges are derived on the basis of the in-solution IEF-PCM/B3LYP/aug-cc-pvtz molecular electrostatic potentials. Relative solute activity coefficients in 0.11 molar aqueous and dichloromethane solutions were predicted as 1.4 and 0.8, respectively. The values refer hypothetical states where only one structural form of the tautomeric pair was considered in the solution model box. A method has been outlined where contributions to the change of the solvation free energy by terms related to relative activity coefficients might be assessed at physically relevant concentrations for the equilibrated tautomers.

The formaldoxime/nitrosomethane equilibrium is very much shifted toward the oxime form with relative internal free energy of more than 12 kcal/mol in favor of this tautomer. The solvent effect leaves this difference or even increases it when  $\Delta\mu^0(\text{tot})$  is calculated. Consideration of the  $\Delta\mu^0(\text{solv})$  term in comparison with  $\Delta\mu^0(\text{int})$  is important, however, in cases, e.g., of the keto–enol or the neutral/zwitterion tautomerism for acetylacetone<sup>48</sup> or isonicotinic acid,<sup>19</sup> respectively, where the two contributions to  $\Delta\mu^0(\text{tot})$  are of similar magnitude with opposite signs.

## ■ ASSOCIATED CONTENT

**S Supporting Information.** Detailed relative solvation free energy terms in water, methanol and dichloromethane solvents as calculated by means of the IEF-PCM method are summarized in Table S1. Table S2 includes derived atomic charges in methanol. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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