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## Chapter 15

# Modeling Free Energies of Solvation and Transfer

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The free energy of transfer of a solute from one medium to another, which is the free energy of solvation if the first medium is the gas phase and the second is a liquid-phase solution, controls all solvation and partitioning phenomena. The SM5.4 quantum mechanical solvation model allows for the calculation of (i) partitioning free energies between the gas phase and a solvent (i.e., free energies of solvation) or (ii) partitioning free energies between two solvents. The model provides a framework for interpreting the factors responsible for differential solvation effects and can be used to predict solvation effects on chemical equilibria and kinetics—examples in this chapter include partitioning of the nucleic acid bases between water and chloroform, solvation effects on anomeric conformational equilibria, and solvation effects on the rate of the Claisen rearrangement.

A collection of solute molecules will partition between two (or more) phases so as to equalize the concentration-dependent chemical potential of the solute in all phases (1). This behavior has far reaching consequences in chemistry. For instance, a molecule might have very high specific activity against a target enzyme, but if its concentration in aqueous biophases or fatty tissues is extremely low it may be inefficacious as an oral drug (since it must be carried by the bloodstream and, if the enzyme is located intracellularly, it must pass through a lipid bilayer membrane). A second example of medium effects on equilibria is that the fraction of molecules in any one of several potentially accessible conformations can depend significantly on solvent, and this structural equilibrium may have significant effects on molecular properties, recognition, and reactivity. As a final example, medium effects on reaction rates can be viewed as changes in the relative equilibrium concentrations of reactants and activated complexes on going from one environment to the next. These examples

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illustrate the practical importance of being able to predict concentrations for solutes in different media.

In an ideal solution, the chemical potential  $\mu$  for a solute in a given medium can be expressed as (1)

$$\mu = \mu^{\circ} + RT \ln \left( \frac{X}{X^{\circ}} \right) \quad (1)$$

where  $\mu^{\circ}$  and  $X^{\circ}$  are the standard state chemical potential and concentration, respectively, for the solute in the medium, and  $X$  is the concentration of the solute. For a solute in equilibrium between two phases  $i$  and  $j$ , equality of the chemical potentials implies that

$$\mu_i^{\circ} - \mu_j^{\circ} = RT \ln \left( \frac{X_i^{\circ}}{X_j^{\circ}} \right) - RT \ln \left( \frac{X_i}{X_j} \right). \quad (2)$$

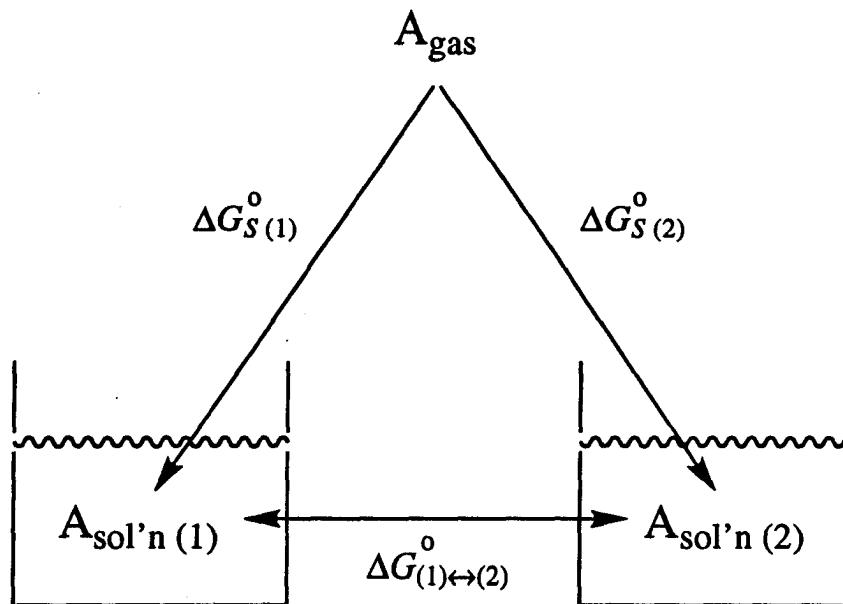
In practice, the standard state concentrations are typically chosen to be the same in both phases so that the first term on the right-hand-side is zero, in which case one recovers the well known

$$\Delta G_{j \rightarrow i}^{\circ} = -RT \ln \left( \frac{X_i}{X_j} \right). \quad (3)$$

That is, the standard state free energy of transfer from phase  $j$  to phase  $i$  is proportional to the logarithm of the ratio of concentrations of the solute in the two phases (sometimes also written  $\Delta G_{ij}^{\circ}$ ; the equilibrium constant for the transfer is called the "partition coefficient"). From an experimental standpoint, this means that the standard state free energy of transfer can be determined by measuring the concentration of substrate in each of the two phases at equilibrium under ideal-solution conditions (which typically requires low concentrations in both phases). From the theoretical standpoint, a model that predicts the standard state free energy of transfer also permits the prediction of differential substrate concentrations between the two phases.

The SMx series of quantum mechanical solvation models are designed specifically to calculate standard state free energies of transfer between the gas phase and solution (2-15). By appropriate use of thermodynamic cycles as illustrated in Figure 1, this also allows for the calculation of free energies of transfer between two *different* solutions.

This chapter focuses on a particular member of the SMx family, namely the SM5.4 model. This model has specific parameters for water (12), chloroform (15), benzene and toluene (16), and a general set of parameters that can be used for any other organic solvent (14). The SM5 part of the name refers to the solute-geometry-



**Figure 1.** Free energy cycle for transfer of A from the gas phase into either of two solvents or between the two solvents. Since the complete cycle must sum to zero, knowing any two sides of the triangle permits calculation of the remaining side.

dependence assumed for first-solvation-shell effects, and the “.4” in the model name indicates that the electrostatic portion of the solvation free energy is calculated using Class IV atomic partial charges (6,17) (vide infra). In this chapter we use the water, chloroform, benzene, and toluene parameters wherever applicable and the general organic parameters otherwise.

#### Solvation Model 5.4

The functional forms for the SM5.4 model have been presented in full detail in the elsewhere (12,14,15). In this section we review those features of the models that are important to understanding the rest of this chapter.

**Framework of Model.** The free energy of solvation is partitioned into two terms (2,5,18-20)

$$\Delta G_S^o = \Delta G_{\text{ENP}} + G_{\text{CDS}} \quad (4)$$

where  $\Delta G_{\text{ENP}}$  includes the change in the electronic and nuclear internal energy of the solute and the electric polarization free energy of the solute-solvent system upon

insertion of the solute into the solvent, and  $G_{\text{CDS}}$  is the contribution of first-solvation-shell effects to the standard-state free energy of transfer. Note that the S in  $\Delta G_{\text{S}}^{\circ}$  stands for solvation, ENP stands for electronic-nuclear-polarization, and CDS stands for cavitation-dispersion-solvent-structure. All SMx models use a standard state of 298 K and 1 M in both the gas phase and solution.

The  $\Delta G_{\text{ENP}}$  term, which is often called the electrostatic term, can be further decomposed as

$$\Delta G_{\text{ENP}} = \Delta E_{\text{EN}} + G_{\text{P}} \quad (5)$$

where  $\Delta E_{\text{EN}}$  is the change in the electronic and nuclear energy of the solute in going from the gas phase to solution, and  $G_{\text{P}}$  is the polarization free energy. The terms in equation 6 are calculated based on neglect of diatomic differential overlap molecular orbital theory using either the Austin Model 1 (21-23) (AM1) or Parameterized Model 3 (24) (PM3) Hamiltonian; these choices are distinguished by the notations SM5.4/AM1 and SM5.4/PM3, respectively.

$G_{\text{P}}$  is calculated from Class IV atomic charges  $q$  using the AM1 or PM3 wave functions and Charge Model 1A (17) or Charge Model 1P (17), respectively, according to

$$G_{\text{P}} = -\frac{1}{2} \left( 1 - \frac{1}{\epsilon} \right) \sum_{k,k'} q_k q_{k'} \gamma_{kk'} \quad (6)$$

where  $\epsilon$  is the solvent dielectric constant,  $k$  and  $k'$  label atoms, and  $\gamma_{kk'}$  is a Coulomb integral that accounts for either the self-energy of a charge in a dielectric medium ( $k=k'$ ) or the screened Coulomb interaction of two charges ( $k \neq k'$ ). Computation of  $\gamma_{kk'}$  involves the use of atomic Coulomb radii  $\rho_k$ ; these Coulomb radii are parameters originally optimized for water (12) and the same values are used in all SM5.4 parameterizations discussed here. Although the accuracy of the SM5.4 model is fairly insensitive to the atomic Coulomb radii, the magnitudes of the ENP and CDS components of the free energy of solvation are more sensitive. Final radii were selected based on careful inspection of various classes of solutes to ensure physically meaningful ENP values. These intrinsic radii are modified in molecular calculations by an algorithm that accounts for descreening of solute atoms (i.e., displacement of the dielectric screening of the surrounding medium) by the molecular volume of the solute (2,11,25).

The first-solvation-shell term has the general form:

$$G_{\text{CDS}} = \sum_k \sigma_k A_k (R_{\text{S}}^{\text{CD}}) + \sigma^{\text{CS}} \sum_k A_k (R_{\text{S}}^{\text{CS}}) \quad (7)$$

where  $k$  denotes an atom,  $A_k(R_{\text{S}}^{\text{CX}})$  is the solvent-accessible surface area (11,26) of atom  $k$  as calculated for a rolling solvent ball having radius  $R_{\text{S}}^{\text{CX}}$ , and the various  $\sigma$  are surface tensions (having units of energy per unit area). The atomic surface tensions  $\sigma_k$  typically depend upon the local geometry of the solute and one or more

surface tension coefficients  $\delta_{Z_k}^i$  that are themselves dependent on the atomic number  $Z$  of atom  $k$  and are parameters of the model, i.e.,

$$\sigma_k = f_{Z_k}(\mathbf{R}, \{\hat{\sigma}_{Z_k}^i\}) \quad (8)$$

where  $\mathbf{R}$  denotes the solute geometry and the set of functions  $f_k$  that define the SM5 set of models has been described in detail (12-15). The molecular surface tension  $\sigma^{\text{CS}}$  is a constant for a given solvent.

We note that in the parameterization of *all* SM5.4 models, solute geometries and electronic wave functions were allowed to fully relax in response to surrounding solvent. All surface tension coefficients are different (separately optimized) for SM5.4/AM1 and SM5.4/PM3, but other parameters are the same for the /AM1 and /PM3 cases.

**Parameterization for water (12).** The dielectric constant employed in equation 6 is 78.3. In the SM5.4-water model, the solvent radii  $R_S^{\text{CD}}$  and  $R_S^{\text{CS}}$  are both taken to be 1.7 Å, so that equation 8 simplifies to

$$G_{\text{CDS}} = \sum_k \sigma_k A_k(R_S). \quad (9)$$

Thus,  $\sigma^{\text{CS}}$  is not a separately optimized parameter in the SM5-water model, but is absorbed into the optimization of the atomic surface tension coefficients contributing to each  $\sigma_k$ . The Coulomb radii and surface tension coefficients were optimized against a set of 34 ionic and 215 neutral experimental free energies of aqueous solvation. Table I provides information on the accuracy of the model.

**Parameterization for general organic solvents (14).** The hallmark of the general SM5.4 model is that it is designed to be employed for *all* organic solvents. In order to accomplish this, the molecular surface tension appearing in equation 7 and the atomic surface tension coefficients appearing in equation 8 are taken to be functions of experimental *solvent* properties. In particular,

$$\sigma^{\text{CS}} = \sigma^{\text{CS},n} + \sigma^{\text{CS},\gamma} \gamma \quad (10)$$

$$\hat{\sigma}_{Z_k}^i = \hat{\sigma}_{Z_k}^{i,n} + \hat{\sigma}_{Z_k}^{i,\alpha} \alpha + \hat{\sigma}_{Z_k}^{i,\beta} \beta \quad (11)$$

where  $n$  is the solvent index of refraction,  $\gamma$  is the macroscopic solvent surface tension, and  $\alpha$  and  $\beta$  are Abraham's (27-29) indices of solvent hydrogen bonding acidity and basicity, respectively (more specifically, these are the  $\Sigma\alpha_2^{\text{H}}$  and  $\Sigma\beta_2^{\text{H}}$  values for a solvent molecule were it to be taken as a *solute* in the Abraham model). The solvent radii  $R_S^{\text{CD}}$  and  $R_S^{\text{CS}}$  are taken to be 1.7 and 3.4 Å, respectively. Two radii appear to be required in order to accurately capture both short-range (cavitation-dispersion) and intermediate-range (cavitation-solvent-structure) effects—for the

**Table I.** Calculated mean signed errors (MSE), mean unsigned errors (MUE), and root-mean-square errors (RMS) for solvent/gas molar free energies of transfer using SM5.4 solvation models (kcal).

Solvents	Solutes	AM1			PM3		
		MSE	MUE	RMS	MSE	MUE	RMS
Water	ions <sup>a</sup>	0.0	4.1	5.6	0.1	4.2	5.6
	neutrals <sup>b</sup>	0.0	0.5	0.8	0.0	0.5	0.6
Chloroform	neutrals <sup>c</sup>	0.1	0.5	0.7	0.0	0.4	0.5
Benzene	neutrals <sup>d</sup>	0.2	0.5	0.8	0.2	0.4	0.5
Toluene	neutrals <sup>e</sup>	0.1	0.3	0.4	0.2	0.3	0.4
General organic	neutrals <sup>f</sup>	-0.1	0.5	0.6	-0.1	0.4	0.6

<sup>a</sup> 34 data points for both AM1 and PM3. Fitted values range from -55 to -107 kcal.

<sup>b</sup> 215 data points for AM1, 214 for PM3. Fitted values range from 4 to -11 kcal.

<sup>c</sup> 88 data points for both AM1 and PM3. Fitted values range from 0 to -13 kcal. <sup>d</sup> 60 data points for AM1, 59 for PM3. Fitted values range from 0 to -8 kcal. <sup>e</sup> 45 data points for both AM1 and PM3. Fitted values range from 0 to -8 kcal. <sup>f</sup> 1599 data points for AM1, 1597 for PM3. Fitted values range from 2 to -15 kcal.

alkane models, the magnitudes of the CD and CS terms are consistent with available data for cavitation and dispersion energies (9).

The set of surface tension coefficients  $\delta_{Z_k}^{i,j}$  together with  $\delta^{CS,\gamma}$  were optimized against a set of 1786 experimental free energies of transfer from the gas phase into various organic solvents (either measured directly or derived from solvent/solvent partition coefficients and solvent/gas solvation free energies according to the scheme illustrated in Figure 1). These data spanned 206 different solutes and 90 different organic solvents (including chloroform, benzene, and toluene). Table I provides information on the accuracy of the model. The errors in Table I for this parameterization do not include the chloroform, benzene, and toluene data points; inclusion of these points affects the errors by less than 0.1 kcal, but we want to emphasize that for calculations in these solvents the specific parameterizations are nearly always to be preferred.

**Parameterization for chloroform (15).** The dielectric constant employed in equation 6 is 4.2. The solvent radii  $R_S^{CD}$  and  $R_S^{CS}$  are taken to be the same as in the general organic model. The atomic surface tension coefficients and the molecular surface tension were optimized against a set of 88 experimental free energies of transfer from the gas phase to chloroform (either measured directly or derived from chloroform/water partition coefficients and gas/water solvation free energies according to the scheme illustrated in Figure 1). In addition, the optimization was restrained by (i) including data for 123 free energies of solvation into solvents other than chloroform for molecules containing functional groups poorly represented in the chloroform data and (ii) including data for 26 chloroform water partition coefficients

where the free energies of aqueous solvation were calculated using SM5.4-water. The restraint is based on the solvent dependencies of the general organic parameterization discussed above. Table I provides information on the accuracy of the model.

**Parameterizations for benzene and toluene (16).** The dielectric constants employed in equation 6 were standard values (30). The solvent radii  $R_S^{CD}$  and  $R_S^{CS}$  are taken to be the same as in the general organic model. The atomic surface tension coefficients were taken to be the same as in the general organic model with the exception of  $\sigma^{CS,\gamma}$ , the magnitude of which was reduced by 34% and 23% for benzene and toluene, respectively; these factors were optimized against sets of experimental free energies of transfer from the gas phase to the aromatic hydrocarbon solvent (free energies either measured directly or derived from solvent/water partition coefficients and gas/water solvation free energies according to the scheme illustrated in Figure 1). Table I provides information on the number of data and the accuracy of the models.

**Interpreting ENP and CDS components.** An important aspect of the various SM5.4 parameterizations is that considerable care went into ensuring that the various parameter values and the individual terms in equation 4 are physically meaningful. This involved a certain degree of chemical intuition, since the ENP and CDS components are not state functions like their sum (20). In addition, special care was paid to subsets of the parameterization data organized by solute functional group(s) to attempt to minimize any systematic bias in the models, and trends in parameter values were examined to determine if they were consistent with expected trends based on chemical behavior. For example, one would expect SM5.4 surface tension coefficients  $\sigma_{Z_k}^{i,n}$  associated with the index of refraction (a measure of solvent polarizability) to become increasingly negative with increasing atomic polarizability (i.e., dispersion interactions will become more favorable for these atoms), and indeed that trend is observed (14). Similar trends over groups having varying degrees of hydrogen bond donating and accepting capabilities are also observed (14). So, while the separation of ENP and CDS contributions is necessarily ambiguous, we believe that the parameter sets yield physically meaningful terms and provide for an additional level of detail that may be analyzed from an SM5 calculation.

### Partition Coefficients

For many interesting solutes, lack of volatility makes the measurement of gas/solvent transfer free energies difficult. One example of biological interest is that of the methylated nucleic acid bases (Figure 2). For such solutes, experimental data are more typically available in the form of solvent/solvent partition coefficients. In the case of the methylated nucleic acid bases, chloroform/water partition coefficients are available for six cases (31). Table II is a compilation of experimental values (when available) and predicted values from two models. In particular, the SM5.4 results are compared to published work of Orozco et al. (32) using the Miertus-Scrocco-Tomasi (33-36) algorithm for electrostatics plus semiempirical surface tensions parameterized specifically for chloroform by Luque et al. (36). We note that the mean unsigned

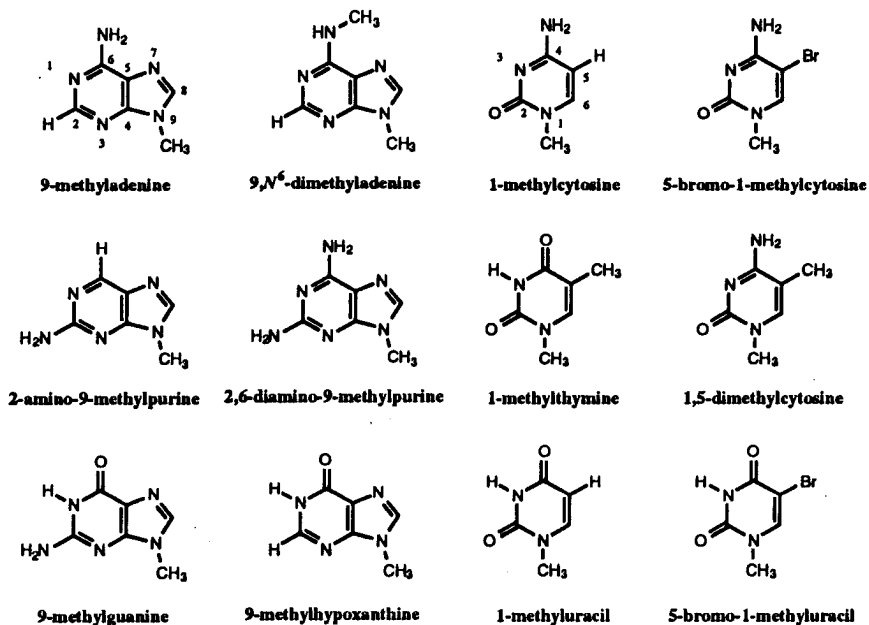


Figure 2. Methylated nucleic acid bases.

Table II. Chloroform/water partition coefficients ( $\log_{10}$  units) for methylated nucleic acid bases.<sup>a</sup>

Solute	SM5.4	MST/ST	Experiment
9-Methyladenine	-1.7	-0.3	-0.8
9, <i>N</i> <sup>6</sup> -Dimethyladenine	-0.3		
2-Amino-9-methylpurine	-1.9		
2,6-Diamino-9-methylpurine	-2.4		
9-Methylguanine	-4.1	-4.8	-3.5
9-Methylhypoxanthine	-3.6	-1.4	-2.5
1-Methylcytosine	-4.2	-3.4	-3.0
5-Bromo-1-methylcytosine	-2.4		
1-Methylthymine	-0.3	-0.4	-0.5
1,5-Dimethylcytosine	-3.1		
1-Methyluracil	-1.2	-1.0	-1.2
5-Bromo-1-methyluracil	-0.3		
<i>Mean unsigned error:</i>	<i>0.6</i>	<i>0.6</i>	

<sup>a</sup> All calculations used the AM1 Hamiltonian.



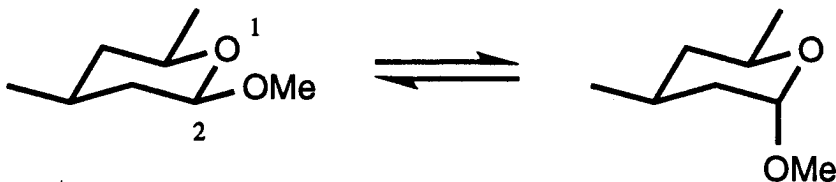
error comparing the SM5.4 partition coefficients to experiment is only 0.6 log units. [Applying the general organic parameters for chloroform (as opposed to the chloroform-specific ones) makes every chloroform free energy of solvation slightly more negative and decreases the mean unsigned error to 0.5 log units, which is also very respectable and comparable to the results obtained with the MST/ST specific chloroform/water models. The difference seems to be primarily a consequence of a less positive  $\sigma^{\text{CS}}$  value for chloroform in the general organic model.]

One advantage of the generalized Born approach, compared to other continuum models, is that solvation free energies (and partition coefficients) can be rather simply decomposed into contributions from individual molecular fragments, e.g., functional groups. This permits an analysis of such issues as the transferability of group contributions to partition coefficients for different chemical environments, and we have examined this elsewhere for the specific case of the methylated nucleic acid bases discussed above (37).

### Solvent Effects on an Anomeric Equilibrium

Stereoelectronic effects on conformational equilibria are another example of a thermochemical phenomenon that may have a large medium effect. A classic example is the anomeric effect. The term "anomeric effect" refers to the unexpectedly low energies of pyranose and pyranoside structures with axial substituents at the anomeric, i.e., C(2), position (Figure 3) (38-44); this stability is unexpected insofar as axial substituents on six-membered rings typically experience strong destabilizing steric interactions with other axial C-X bonds. The stabilization, unique among six-membered rings to the pyranoses, pyranosides, and analogs, has been rationalized as arising from decreased dipole-dipole repulsion between C-O bonds in the axial anomer (45-47) and/or from greater hyperconjugative stabilization of the pyranose oxygen lone pair when delocalized into the empty axial  $\sigma_{\text{CO}}^*$  orbital (48-51). The degree to which these two phenomena contribute to the free energy in any given system (or the degree to which it is profitable to single out either of these two explanations for the single physical effect) depends on the molecular structure (42,52-61) and, importantly, also the surrounding medium (42,44,54,61-74).

In this section, we compare predictions of the SM5.4 model (using the PM3 Hamiltonian and fully relaxed geometries—AM1 results are quantitatively very similar) to experiment for the effect of solvation on the anomeric equilibrium of



**Figure 3.** The anomeric equilibrium for 2-methoxy-4,6-dimethyltetrahydropyran.

**Table III.** Solvent effect (kcal) on the molar free energy of anomerization of 2-methoxy-4,6-dimethyltetrahydropyran.

Solvent	OPLS <sup>a</sup>	SM5.4/PM3	Expt. <sup>b</sup>	Other expt. <sup>c</sup>
benzene		0.4	0.2	0.0–0.2
CCl <sub>4</sub>	0.1	0.4	0.3	0.1–0.3
<i>n</i> -butyl ether		0.5	0.3	
DMSO		0.8	0.5	0.3–0.4
acetone		0.7	0.5	0.3–0.4
pyridine		0.7	0.6 <sup>d</sup>	
methanol		0.7	0.7	0.5–0.7
acetonitrile	1.6	0.7	0.7	0.5–0.7
water	2.1	0.6		0.9

<sup>a</sup> Reference (72). <sup>b</sup> Reference (71). <sup>c</sup> Reference (58). <sup>d</sup> Change in enthalpy, not free energy.

2-methoxy-4,6-dimethyltetrahydropyran. Wiberg and Marquez have performed thermochemical measurements of the solvation effect on this anomeric equilibrium (71), and those results are provided in Table III. Also included is a summary of solvation effect data compiled by Tvaroska and Carver (58) for 2-methoxytetrahydropyran, 2-methoxy-6-methyltetrahydropyran, 2-methoxy-4-methyltetrahydropyran, and 2-ethoxytetrahydropyran. Finally, Jorgensen et al. have modeled solvation effects on the anomeric equilibrium of 2-methoxytetrahydropyran using a Monte Carlo statistical model with explicit solvent and the OPLS force field (72), and their predictions are also provided in Table III. All of the values in Table III are positive free energies, implying a preferential solvation of the equatorial anomer.

An inspection of the SM5.4 results suggests that there is a systematic overestimation of the solvation effect (i.e., the equatorial anomer is oversolvated relative to the axial) by about 0.2 kcal in most organic solvents. In water, on the other hand, the SM5.4 prediction is 0.3 kcal smaller than that found experimentally (64). Nevertheless, the overall agreement between the SM5.4 results and experiment is encouraging, especially when one considers alternative models. The much more expensive OPLS simulations of Jorgensen et al. (72) appear to strongly oversolvate the equatorial anomer in acetonitrile and water. Similarly, using a continuum solvent model that considered *only* electrostatic effects, Montagnani and Tomasi calculated the equatorial anomer to be better solvated than the axial by 0.6 kcal in CCl<sub>4</sub> and 1.4 kcal in water (65). One might infer from these latter results, which overestimate the effect of solvent on the anomeric equilibrium, that non-electrostatic effects oppose electrostatic effects in their influence. With the SM5.4 models, however, we do not find a significant difference between the CDS components of the free energies of solvation for the two anomers. The sensitivity of  $\Delta G_{\text{ENP}}$  to geometry relaxation for each anomer, on the other hand, is particularly noteworthy. For instance, with frozen PM3 gas-phase structures, the calculated solvation effect on the anomeric equilibrium

is doubled compared to using relaxed structures; this difference is found entirely in  $\Delta G_{\text{ENP}}$ . When MP2/cc-pVDZ gas-phase geometries were used, the quality of the predictions was also degraded by about the same magnitude. This example illustrates how difficult it can be to assess the quality of a given theoretical approach in the absence of experimental data against which to validate different approximations, e.g., choice of geometry, choice of solvation model, etc., particularly when the range of solvent effects being compared spans less than 1.0 kcal/mol.

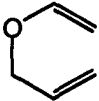
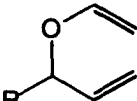
### Solvent Effects on the Rate of the Claisen Rearrangement

The [3,3]-sigmatropic shift of an allyl vinyl ether to produce a 4-pentenal is called the Claisen rearrangement (75). This reaction has attracted considerable attention primarily because in a number of organisms it is the mechanism by which chorismate rearranges to prephenate in the committed step for the biosynthesis of aromatic amino acids (76,77). In an effort to better understand the function of the enzyme involved much work has appeared in the area of molecular biology (78-80), and, in addition, experimental studies have investigated the character of the transition state by examination of substituent and solvent effects on the rate of the rearrangement (81-86). Based on rate accelerations observed in polar solvents and sensitivity to substituent positioning, there is consensus (81-86) that the transition state has greater charge separation than the reactant, and that negative charge concentrates on the oxygen atom, so that hydrogen-bonding solvents accelerate the reaction. Theory is entirely in concert with this analysis, with studies having been done with both continuum (6,87-92) and explicit solvent models (88,93-98), as well as simulations including the enzyme catalyst (98). The SM5.4 model, being quantum mechanical, is well suited to calculations on transition states, and it is interesting to apply it to this problem.

We have previously examined (6) aqueous acceleration of the Claisen rearrangement for allyl vinyl ether using a SM4 water model with specific range parameters (i.e., parameters chosen for a subset of molecules bearing some similarities to those involved in the rearrangement, in this case aldehydes, ethers, and hydrocarbons). That study demonstrated how sensitive the rate acceleration is to the looseness of the transition state, and we found that using a transition state structure calculated at the multiconfigurational SCF level (99) gives good agreement between theory and the experimental rate acceleration in water, which is estimated to be about  $1 \times 10^3$  (93). Here we examine the same rearrangement using the same reactant and transition state structures as before, but with SM5.4, which allows us to compare to the study of Brandes et al. (85), which examined the effect of solvation over a broad range of solvents by comparing the reaction rates for two different substituted Claisen substrates (see Table IV). In solvents where both reactants were soluble, the rates were identical to within a factor of two, allowing a "ladder" to be constructed from cyclohexane to water. Those results, together with the SM5.4 predictions, are presented in Table IV.

The predicted accelerations relative to cyclohexane using SM5.4 are good for benzene and trifluoroethanol. The aqueous acceleration is underestimated, although a factor of 4 represents an error of only 0.8 kcal/mol. On the other hand, the rates in

Table IV. Relative rates for Claisen rearrangements in different solvents.

Solvent		
	SM5.4/AM1 <sup>a</sup>	Experiment <sup>b</sup>
cyclohexane	1.0	1.0
benzene	1.3	2.0
methanol	57.9	8.6
trifluoroethanol	56.6	56.0
water	53.7	214.3

<sup>a</sup> 298 K. <sup>b</sup> R = (CH<sub>2</sub>)CO<sub>2</sub>Me for organic solvents and (CH<sub>2</sub>)CO<sub>2</sub>Na for water. All results for 333 K.

methanol and trifluoroethanol are predicted to be essentially the same, whereas experimentally they differ by a factor of 7. There are a number of possible explanations for this discrepancy, but, based on results from molecular simulations (88,93), the most likely explanation is that specific solvation in the form of hydrogen bonding to the oxygen atom can modify the overall transition state structure in a way not well accounted for in the MCSCF structure. In the general case, this situation does not pose a special problem for a continuum model like SM5.4 in one can include the special solvent molecule(s) and consider the continuum solvation of the supersolute. However, for the present case, reoptimization of the transition state structure at the semiempirical level is not an option since AM1 does not provide an adequate description of the gas-phase transition state structure. It will be interesting to revisit this system when the SMx models are extended to ab initio levels of theory, in particular density functional theory, since Houk and co-workers have found this level of theory to give excellent Claisen transition state structures based on analysis of kinetic isotope effects (100).

### Conclusions

The SM5.4 solvation model provides a robust general method for the quantum mechanical calculation of organic and aqueous solvation effects on a variety of chemical phenomena. Partition coefficients can be predicted, and the total partition coefficient can be decomposed into atomic or group contributions—this should prove particularly useful in the area of molecular design, e.g., for pharmaceutical purposes or to enhance nonlinear optical effects. Computation of differential solvation effects for isomers (conformational, tautomeric, or structural) and for reactants vs transition state structures permits prediction of solvent-induced changes in equilibrium and rate constants, respectively. The physical separation of electrostatics from first-solvation-

shell effects allows chemical interpretation of these phenomena, although care is warranted when the effects become small so that the model is not overinterpreted.

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### Additional Information.

Further details about the SMx solvation models and software implementing them may be found at <http://amsol.chem.umn.edu/~amsol>.

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