1489, and 1431 cm^{-1}, the broad C–O stretching peak at 1278 cm^{-1}, and the broad phenolic O–H stretching peak centered at 3342 cm^{-1}. The small peaks between 2975 and 2850 cm^{-1} are due to a small amount of hydrocarbon contamination. The top part of Figure 2 shows the spectrum for the 4-HTP surface after exposure to the silane. In the high-frequency region, the phenolic O–H band originally present at 3342 cm^{-1} has disappeared, and stronger absorptions between 2975 and 2850 cm^{-1} indicate the presence of the hydrocarbon portion of the silane coupling agent. In the low-frequency region, the somewhat enhanced aromatic ring stretches are still present at 1585 and 1486 cm^{-1},[8] but there is a new absorption at 918 cm^{-1} arising from the symmetric Si–phenoxy stretching mode of the reaction product, Scheme I.[9] The two overlapping bands at 1277 and 1260 cm^{-1} result from the asymmetric Si–phenoxy stretch and the symmetric H_3C–Si–CH_3 deformation, respectively.[9]

Ellipsometric results[4] are in accord with the SAW and FTIR-ERS experiments. The average measured thickness of three vapor-deposited 4-HTP layers is 5.8 ± 0.8 Å, which increases to 12.5 ± 1.2 Å after reaction with $[CH_3(CH_2)_7](CH_3)_2SiCl$. Similar results are found for surface-confined 4-ATP before (7.4 ± 0.9 Å) and after (12.1 ± 1.2 Å) exposure to $[CH_3(CH_2)_7](CH_3)_2SiCl$. These data show that both reactants and products are present at approximately monolayer coverage. Since we do not know the orientation of the adsorbates, it is difficult to infer theoretical thicknesses for the organic monolayers, but the trend toward thicker layers is expected.

To summarize, we have demonstrated that well-characterized reactions occur between surface-confined monolayers and vapor-phase reactants at atmospheric pressure. These reaction conditions provide an important link between solution and ultra-high-vacuum studies. Real-time SAW experiments, FTIR-ERS, and ellipsometry demonstrate that the vapor-phase coupling reactions between surface-confined 4-HTP or 4-ATP and $[CH_3(CH_2)_7](CH_3)_2SiCl$ result in monolayer coverages of stoichiometric reaction products. Moreover, experiments with other coupling agents, $[CH_3(CH_2)_n](CH_3)_2SiCl$ (n = 0, 2), show appropriate attenuations in mass, methylene stretching absorption intensity, and thickness, further supporting our conclusions. At present, we have no evidence that either the reactants or products are highly organized, but experiments are in progress to extend this study to other vapor-phase coupling reactions that may lead to such structures.

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Registry No. Au, 7440-57-5; $[CH_3(CH_2)_7](CH_3)_2SiCl$, 18162-84-0; 4-HTP, 637-89-8; 4-ATP, 1193-02-8.

Supplementary Material Available: Details of the SAW, ellipsometry, and synthesis and spectral characterization of solution analogues of the surface-confined reactants and products (5 pages). Ordering information is given on any current masthead page.

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Molecular Orbital Theory Calculations of Aqueous Solvation Effects on Chemical Equilibria

Christopher J. Cramer*

U.S. Army Chemical Research Development and Engineering Center
Aberdeen Proving Ground, Maryland 21010-5423

Donald G. Truhlar*

Department of Chemistry, Supercomputer Institute, and Army High-Performance Computing Research Center
University of Minnesota
Minneapolis, Minnesota 55455-0431
Received July 16, 1991

Molecular modeling techniques[1] have advanced to the point where computational chemistry can predict the relative energies of many interesting structures, intermediates, and possible reaction products. Parametric models[2-4] based on semiempirical molecular orbital theory are especially useful for treating substituent effects and evaluating competing structures; for reactions in aqueous solution, though, there is considerably uncertainty about the applicability of the calculated results since the computational models do not include the solvent. One way to improve on this situation is to combine these models with the local-field SCF approach.[5] In this spirit, we have recently proposed and calibrated a new parameterized model,[6] called AM1-SM1, in which an aqueous "solvation model" (SM1) is added to the Fock operator from neglect-of-diatomic-differential-overlap[7] semiempirical molecular orbital theory using the Austin model 1 (AM1)[3] parameterization for the solute. SM1 treats the solvent as a bulk continuum with a generalized Born model[8,9] with dielectric screening for the polarization energy (we use a model in which the solute cavity from which dielectric is excluded is composed of superimposed spheres[9,10]) and with surface tension terms[11] (based on the solvent-accessible surface area[12]) for cavity and dispersion effects. Parameters are available[6] for 298 K for solutes containing H, C, N, O, F, S, Cl, Br, and I. The theory is especially promising because it requires considerably less in the way of computational resources than simulations with explicit inclusion of a large number of water molecules,[13] yet *at the same time* it allows for solvent-induced changes in the solute charge distribution.

Here we report the first tests of AM1-SM1 for the effect of solvation on reactive equilibria, in particular for acid–base proton transfer reactions, prototropic tautomerizations, and the rotameric isomerization of the peptide linkage. We define

$$\Delta\Delta G^\circ_{g\to aq} = \Delta G^\circ_{aq} - \Delta G^\circ_{g} \qquad (1)$$

where ΔG° is the standard-state (1 M) free energy change for

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Table I. Proton Transfer Free Energy Changes on Solvation

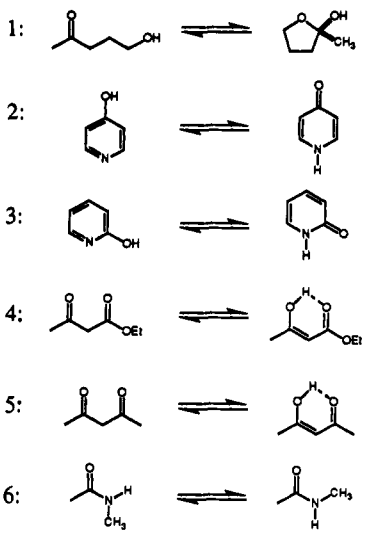
reaction	$\Delta\Delta G_{g\to aq}$, kcal/mol: expt[a]	AM1-SM1
NH_4^+ + aniline → NH_3 + aniline·H^+	12.9	19.0
NH_4^+ + $MeNH_2$ → NH_3 + $MeNH_3^+$	9.6	11.3
NH_4^+ + pyridine → NH_3 + pyridine·H^+	25.1	25.9
NH_4^+ + Me_2NH → NH_3 + $Me_2NH_2^+$	17.6	20.6
NH_4^+ + Me_3N → NH_3 + Me_3NH^+	23.7	28.8
NH_4^+ + $PhCO_2^-$ → NH_3 + $PhCO_2H$	137.3	146.4
NH_4^+ + AcO^- → NH_3 + AcOH	146.9	151.7
NH_4^+ + PhO^- → NH_3 + PhOH	141.1	143.0
NH_4^+ + Cp^- → NH_3 + CpH[b]	137.6	137.5
aniline·H^+ + $MeNH_2$ → aniline + $MeNH_3^+$	9.6	11.3
aniline·H^+ + pyridine → aniline + pyridine·H^+	25.1	25.9
aniline·H^+ + Me_2NH → aniline + $Me_2NH_2^+$	17.6	20.6
aniline·H^+ + Me_3N → aniline + Me_3NH^+	23.7	28.8
aniline·H^+ + $PhCO_2^-$ → aniline + $PhCO_2H$	124.4	127.4
aniline·H^+ + AcO^- → aniline + AcOH	134.0	132.6
aniline·H^+ + PhO^- → aniline + PhOH	128.2	124.0
aniline·H^+ + Cp^- → aniline + CpH	124.7	118.5
$MeNH_3^+$ + pyridine → $MeNH_2$ + pyridine·H^+	15.5	14.6
$MeNH_3^+$ + Me_2NH → $MeNH_2$ + $Me_2NH_2^+$	8.0	9.4
$MeNH_3^+$ + Me_3N → $MeNH_2$ + Me_3NH^+	14.1	17.4
$MeNH_3^+$ + $PhCO_2^-$ → $MeNH_2$ + $PhCO_2H$	127.7	135.2
$MeNH_3^+$ + AcO^- → $MeNH_2$ + AcOH	137.3	140.4
$MeNH_3^+$ + PhO^- → $MeNH_2$ + PhOH	131.6	131.7
$MeNH_3^+$ + Cp^- → $MeNH_2$ + CpH	128.0	126.2
pyridine·H^+ + Me_2NH → pyridine + $Me_2NH_2^+$	−7.6	−5.3
pyridine·H^+ + Me_3N → pyridine + Me_3NH^+	−1.4	2.9
pyridine·H^+ + $PhCO_2^-$ → pyridine + $PhCO_2H$	112.2	120.6
pyridine·H^+ + AcO^- → pyridine + AcOH	121.8	125.8
pyridine·H^+ + PhO^- → pyridine + PhOH	116.0	117.1
pyridine·H^+ + Cp^- → pyridine + CpH	112.5	111.6
$Me_2NH_2^+$ + Me_3N → Me_2NH + Me_3NH^+	6.2	8.2
$Me_2NH_2^+$ + $PhCO_2^-$ → Me_2NH + $PhCO_2H$	119.7	125.8
$Me_2NH_2^+$ + AcO^- → Me_2NH + AcOH	129.3	131.1
$Me_2NH_2^+$ + PhO^- → Me_2NH + PhOH	123.5	122.4
$Me_2NH_2^+$ + Cp^- → Me_2NH + CpH	121.0	116.9
Me_3NH^+ + $PhCO_2^-$ → Me_3N + $PhCO_2H$	113.7	117.6
Me_3NH^+ + AcO^- → Me_3N + AcOH	123.2	122.9
Me_3NH^+ + PhO^- → Me_3N + PhOH	117.4	114.3
Me_3NH^+ + Cp^- → Me_3N + CpH	114.9	108.7
$PhCO_2H$ + AcO^- → $PhCO_2^-$ + AcOH	9.4	5.3
$PhCO_2H$ + PhO^- → $PhCO_2^-$ + PhOH	3.7	−3.5
$PhCO_2H$ + Cp^- → $PhCO_2^-$ + CpH	1.3	−8.9
AcOH + PhO^- → AcO^- + PhOH	−5.7	−8.6
AcOH + Cp^- → AcO^- + CpH	−8.1	−14.2
PhOH + Cp^- → PhO^- + CpH	−2.4	−5.5

[a] From refs 15 and 17. [b] Cp = cyclopentadienyl (C_5H_5).

the equilibrium in question. In all cases ΔG°_{aq} was calculated by optimizing the structures of reactants and products in aqueous solution with AM1-SM1, and ΔG°_g was computed from gas-phase optimized structures by AM1.[14] Vibrational contributions were assumed to cancel, i.e., to change negligibly upon solvation. A positive $\Delta\Delta G^\circ_{g\to aq}$ value implies that the illustrated equilibrium shifts to the left on solvation, and a negative value implies the opposite.

The results for acid–base equilibria are in Table I, where they are compared to experiment. The latter were obtained by correcting the experimental[15] ΔH^{298}_g proton affinities or deprotonation enthalpies using AM1 calculated absolute entropies[16] to obtain ΔG°_g values and using standard pK_a differences[17] to obtain ΔG°_{aq}.

Table II. Isomerization Free Energy Changes on Solvation



reaction	$\Delta\Delta G^\circ_{g\to aq}$, kcal/mol: expt[a]	AM1-SM1	reaction	$\Delta\Delta G^\circ_{g\to aq}$, kcal/mol: expt[a]	AM1-SM1
1	>4.0	4.1	4	1.4	1.1
2	<−8.0	−8.7	5	1.0	0.9
3	−4.3	−4.4	6	0.0	1.5

[a] See text for references.

The entropic contributions to the gas-phase free energies are, as expected, quite small. From the cyclopentadienyl anion (Cp^-) to ammonia, the substrates span a basicity range of 145.4 kcal/mol in the gas phase, and from Cp^- to benzoate, of 16.3 kcal/mol in solution. The first few examples in Table I illustrate the significantly enhanced basicity of ammonia upon solvation when compared to other amine bases.[18] Similarly, the last three examples illustrate the greater solvation free energies of acetate relative to phenoxide, and phenoxide relative to Cp^-. These effects are well reproduced by AM1-SM1. The root mean square error found for all 45 proton transfers is 4.2 kcal, which is less than 3% of the range of values involved.

Table II summarizes the results for six different isomeric equilibria. In the first case, in the absence of a polar medium, roughly equal populations of the hydroxy ketone and lactol tautomers are observed; in water, however, no lactol is observed.[19] Hydroxypyridine/pyridone equilibria have been extensively studied.[20] Again, detection limits allow only a bound to be set for the 4-substituted isomer. However, AM1-SM1 does quite well with the 2-substituted isomer, for which both gas-phase and solution equilibrium constants are available. Other well-known equilibria where solvation plays a critical role are the enol/ketone equilibria observed for β-keto esters and β-diketones. For both ethyl acetoacetate and acetylacetone, experimental equilibrium constants are available in both the gas and aqueous phases.[21]

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Again AM1-SM1 predicts the $\Delta\Delta G_{g\to aq}$ values accurately. Interestingly, the rotameric equilibrium between the *E* and *Z* forms of *N*-methylacetamide is unaffected by aqueous solvation, i.e., $\Delta\Delta G_{g\to aq} = 0.0$, although $\Delta G_S°$, the free energy of solvation for either isomer, is sizable at -10.0 kcal/mol.[22,23] AM1-SM1 predicts $\Delta G_S°$ for the *E* isomer exactly, but yields only -8.5 kcal for the *Z* isomer, giving a $\Delta\Delta G_{g\to aq}$ of 1.5 kcal.

We conclude that AM1-SM1 has useful chemical accuracy for the effect of hydration on chemical equilibria. We expect that in most cases the dominant error in AM1-SM1 molecular orbital calculations of relative free energies for medium-size organic molecules in aqueous solution will be the error in treating the electronic structure of the solute, not the error in the hydration effect.

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Enantioselective and Diastereoselective Molecular Recognition of Alicyclic Substrates in Aqueous Media by a Chiral, Resolved Synthetic Receptor[1]

Thomas H. Webb, Hongsuk Suh, and Craig S. Wilcox*[,2]

Department of Chemistry, University of Pittsburgh
Pittsburgh, Pennsylvania 15260

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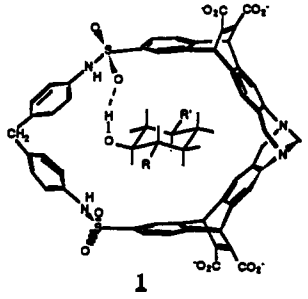
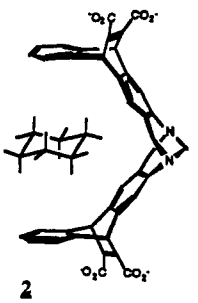
Alkanes have small dipole moments, are of relatively low polarizability, and bear no hydrogen-bonding groups. For this reason, simple alicyclic molecules, when compared to the multiple hydrogen bond forming targets most often studied in contemporary molecular recognition projects, can be characterized as rather reluctant partners in host-guest events. Nevertheless, molecules of this class are often used in natural intraspecies and intracellular communication processes, because alicyclic molecules are especially stable, stereochemically complex, and information-rich.[3] Shape selective receptors for alicyclic molecules could be used in analytical applications, in chromatography, or as agents for the control or catalysis of alicyclic substrate reactivity. Here we describe the synthesis and initial characterization of an optically pure, water-soluble receptor (**1**) that binds stereoselectively to neutral alicyclic targets. The receptor shows immediate promise as a chiral shift reagent for alkanes.



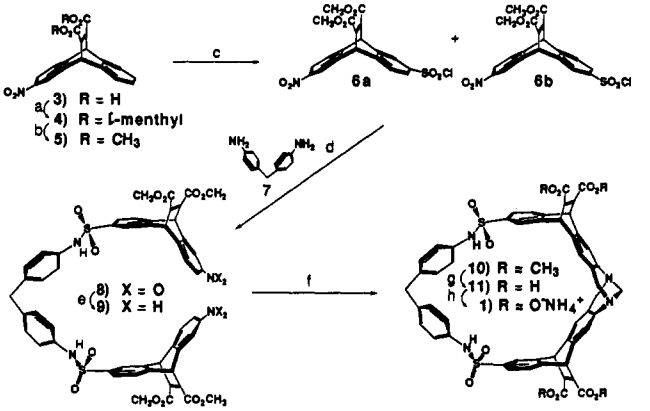
1



2

Since the pioneering work of Whitlock, Koga, Tabushi, and Murakami, cyclophanes have become a well-established class of synthetic receptors for neutral organic targets and have very often been used in studies of binding to *aromatic* substrates.[4,5] Much less often, cyclophane hosts have been used for neutral aliphatic and alicyclic guests or prepared in optically pure form.[6g-i,7] A simple rectangular shape is adequate for binding to benzenoid substrates.[4,8] Receptors for even the simplest aliphatic substrates require a larger pocket. For two benzene rings to bracket a cyclohexane ring, the benzene rings should be separated by about 8.5 Å. Chiral molecular tweezers (**2**) prepared in this lab appear to be well suited for alkane binding but have a disadvantage: water-soluble derivatives of these simple chiral clefts dimerize when in solution.[9]

Scheme I[a]



[a] (a) DCC/CH_2Cl_2, (-)-menthol, then separate diastereomers; (b) concentrated H_2SO_4, then CH_3OH, H^+; (c) $ClSO_3H$; (d) **7**, C_5H_5N; (e) Ni (Raney), then H_2/PtO_2; (f) TFA, hexamethylenetetramine; (g) LiOH, $MeOH/H_2O$; (h) NH_4OH/H_2O.

With these thoughts in mind, we undertook the synthesis of a new chiral and conformationally restricted cyclophane (Scheme I). The racemic nitro acid **3** was resolved through formation of the (-)-menthyl diesters. Crystallization (hexane–ethyl acetate) provided pure diastereomer **4** (mp 186–187 °C).[10] The optically pure dimethyl ester **5**($[\alpha]_D$ = 48.2°) was obtained in 21% overall yield from diacid **3**.[10] Chlorosulfonylation of **5** afforded two regioisomeric sulfonyl chlorides (**6**) in approximately equal amounts. Isomer **6a** was treated with diamine **7** to afford the bis(sulfonamide) **8**. Treatment of diamine **9** in trifluoroacetic acid with hexamethylenetetramine created the dibenzodiazocine unit and provided the macrocyclic tetraester **10** in 28% yield.[11-13]

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