Theoretical Study of the Enol Imine ↔ Enaminone Tautomeric Equilibrium in Organic Solvents

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The tautomeric enol imine ↔ enaminone (phenol ↔ quinone) equilibrium of the 1-hydroxy-2-naphthaldehyde Schiff base (2-phenyliminomethyl-naphthalen-1-ol) was investigated by density functional theory (B3LYP) and ab initio (MP2) methods in the IEF−PCM polarizable continuum dielectric solvent approximation and by a combined ab initio + FEP/MC study by considering an explicit solvent model. Special emphasis was put on the effect of solvation on this equilibrium by using an apolar (CCl_4), polar aprotic (CH_3CN), and polar protic (CH_3OH) solvent. Compared with experimental tautomerization Gibbs free energies, the IEF−PCM/B3LYP calculations apparently overestimate the stability of the quinone form both when the 6-31G(d,p) and the 6-311++G(d,p) basis sets are applied. IEF−PCM/MP2 studies with the above basis sets predict the preference of the aromatic phenol tautomer, in contrast to the experiment in methanol and acetonitrile solvent. Calculation of the total relative free energy as $\Delta G_{tot} = \Delta E_{int}$(IEF−PCM/QCISD(T)/6-31G(d)) + ΔG(solv, FEP/MC) + $\Delta G_{thermal}$ provided agreement with the experimental values up to 0.6 kcal/mol in the three solvents, and the predominant tautomer was always correctly predicted. In-solution relevant atomic charges, derived by a fit to the molecular electrostatic potential generated by the IEF−PCM/B3LYP/6-31G(d,p) wave function, show strong dependence on the fitting procedure (CHELPG or RESP) and are fairly insensitive to the chemical nature of the actual solvent. Use of the CHELPG charges in FEP/MC simulations revealed to be superior in comparison with the use of the RESP charge set.

Introduction

Tautomeric transformations are subject to solvent effects as revealed from the different equilibrium ratios in the gas phase and in solution. In some cases, only the value of the equilibrium constant changes upon solvation but the major gas-phase component remains the predominant component in solution.[1a] In other cases, however, the tautomeric preference switches.[1a,b] Theoretical studies are important for exploring this phenomenon in different solvents[2] because no experimental studies are available for many systems.

Tautomeric changes are extremely important for biological systems. For example, the position of the hydrogen on the ring nitrogen atom of histamine has fueled long scientific debate. Theoretical studies pointed out the significance of the solvent or receptor environmental effect.[3] In a recent study, Nagy et al.[4] investigated the tautomeric equilibria for methyl-substituted five-membered heterocycles with two to four nitrogen atoms in the ring. Such aromatic rings as end groups of an aliphatic chain in a drug molecule can provide different binding abilities in a receptor cavity. The readiness for accepting or rejecting a specific tautomeric form in a moderately polar environment may be decisive with respect to the binding properties of a drug molecule.

Theoretical calculations are difficult when the solvent effect is delicate. Prediction of the predominant tautomer in strongly polar medium is generally possible with widely used methods. More problems emerge when one wants to calculate equilibrium constants at T temperature, K_T, close to the experimental values. Fabian et al.[5a] studied many quinone−enol equilibria in different solvents using the polarizable continuum method[6] at the DFT/B3LYP[7] level. Although the trend for the equilibrium constants in different solvents followed the experimental one, the in-solution K_T values were exaggerated.

When a remarkable difference between the calculated and experimental values is noticed, the adequacy of both the solvation model and the theoretical level is to be reconsidered. To this aim, two different solvation models, continuum dielectric and explicit solvent models, have been applied in the present study. Previous studies for the keto−enol,[8,9c] imine−enamine,[9b,c] and nitro−(aci-nitro)[9a,c] tautomeric equilibria of small systems pointed out that the relative internal energies should be calculated at the G1[10a] or G2[10b] level of theory to obtain results close to the experimental values. The internal energy of vinyl alcohol relative to acetaldehyde in the gas phase was calculated at about 11 and 12 kcal/mol at the G1 and the QCISD(T)[11] levels, respectively.[8] In the gas-phase acetaldimine ↔ vinylamine equilibrium, the relative vinylamine energy is 3.82 and 3.92 kcal/mol at the G1 and G2 levels, respectively.[9b] In studying 1,5-H shift, appearing also through the tautomeric equilibria in the present study, Lammertsma and Bharatam[9c] found that the B3LYP/6-311+G** and G2MP2 relative energies may differ by as much as 5 kcal/mol. Thus, to obtain in-solution equilibrium constants close to the experimental values, high-level estimation of the relative internal energies seems to be necessary.

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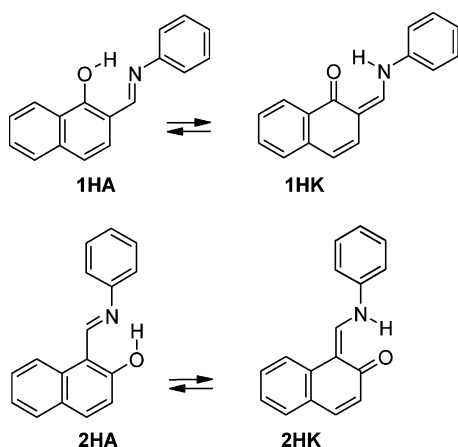
SCHEME 1

In the present investigation, the quinone−enol (enaminone−imino enol, quinone−phenol) 1HA/1HK tautomeric equilibrium has been studied for the 1-hydroxy-2-naphthaldehyde anil (2-phenyliminomethyl-naphthalen-1-ol, Scheme 1) system in methanol, acetonitrile, and carbon tetrachloride. Both tautomers, 1HA and 1HK, are characterized by the presence of a strong intramolecular hydrogen bond. Consequently, compounds showing this type of tautomeric equilibria have been used as model compounds for the theory of hydrogen bonding.[12−14] Besides this significance in basic science, the quinone−enol and the related azo−hydrazo tautomerism[15] of the analogous azo derivatives (CH=N in 1HA/HK replaced by N=N) is of great practical importance, for example, dying properties and light fastness of azo dyes.[16] Molecular geometries have been optimized at the IEF−PCM[6]/B3LYP (polarizable continuum method in the integral-equation formalism) level, and the free-energy perturbation method (FEP)[17] has been applied, as implemented in Monte Carlo (MC) simulations,[18] to calculate relative solvation free energies. The calculated equilibrium constants derived on the basis of the total relative free energies for the tautomers have been compared with experimental values.

Methods and Calculations

Structure of the studied tautomeric pair is shown in Scheme 1. IEF−PCM/B3LYP geometry optimization has been performed at the 6-31G(d,p) level[19] in methanol, acetonitrile, and carbon tetrachloride, using the standard united-atom cavity model in the Gaussian 03 software.[20] Local-minimum-energy character of each structure was certified by all positive vibrational frequencies. Thermal corrections were calculated in the rigid rotor, harmonic oscillator approximation.[21] Single-point calculations at the optimized geometry were performed at the IEF−PCM/B3LYP/6-311++G(d,p), IEF−PCM/MP2/6-31G-(d,p), and IEF−PCM/MP2/6-311++G(d,p) levels.[19] In methanol and acetonitrile, the optimized geometries of the 1HA + CH₃-OH, 1HA + CH₃CN and 1HK + CH₃OH, 1HK + CH₃CN complexes were determined as well. These calculations were performed in order to consider an explicit hydrogen-bond acceptor near the studied structure and explore whether a nearby H-acceptor could compete by forming an intermolecular instead of an intramolecular hydrogen bond (Figure 1).

Relative solvation free energies were calculated through FEP/MC simulations in NpT (isobaric−isothermal) ensembles at $T = 298$ K and $p = 1$ atm[18,22] by running the BOSS 3.6 software.[23] Using the all-atom OPLS-AA 12−6−1 pair potential, the steric (12−6) parameters were taken according to the literature values.[24] Atomic charges were calculated by a fit to the in-

solution ELPO (molecular electrostatic potential) of the optimized molecules at the IEF−PCM/B3LYP/6-31G(d,p) level. ELPO fits were performed by the CHELPG[25] (grid-oriented charges from electrostatic potential) and the RESP[26] (restrained electrostatic potential) procedures.

The solution models were comprised of one solute and 257−260 solvent molecules. Three-point models for each methanol and acetonitrile and a five-point model for carbon tetrachloride were used.[22d,e] Nonphysical reaction paths were selected in the FEP calculations when the phenolic hydrogen was gradually annihilated in 1HA with a concomitant development of the proton on the nitrogen atom of 1HK. The reaction-coordinate parameter, λ, has values of 0 and 1 referring to the chemically correct starting and final structures of the tautomers. Geometric and interaction potential parameters along the transformation path were calculated by linear interpolation between the corresponding starting and end values with λ coupling parameter.[22] The optimized geometries for the tautomers were obtained from IEF−PCM/B3LYP/6-31G(d,p) calculations.

The solvent−solvent cutoff (RCUT) and the solute−solvent cutoff (SCUT) were set to 9.75 Å and 12 Å, respectively. Random translation and rotation for the solute were limited to 0.1 Å and 10°, respectively. Solute trial moves were attempted every 50 steps, while volume alteration (with a maximum of 250 Å³) was attempted every 1000 steps. Periodic boundary conditions and preferential sampling were applied with $c = 120$ in the sampling factor $1/(R^2 + c)$, where R is the distance between the solute's reference atom and the central atom of the selected solvent molecule. With these simulation parameters, 40−60% of the newly generated configurations were accepted out of 3500 K and 5000 K configurations considered in the equilibration and averaging phases, respectively.

The total relative free energy for the tautomeric pair was calculated as

$$\Delta G_{tot} = \Delta E_{int} + \Delta G(solv) + \Delta G_{therm} \qquad (1)$$

where

$$\Delta G(solv) = \Delta G(solv, MC) \qquad (2a)$$

from the FEM/MC simulations or

$$\Delta G(solv) = \Delta G(solv, cont) = \Delta <\psi|1/2V|\psi> + \Delta G_{drc} \quad (2b)$$

V is the self-consistent reaction-field operator and ψ is the corresponding SCF (self-consistent field) wave function in the solution. G_{drc} stands for the nonelectrostatic dispersion-repulsion-cavity formation energy in the corresponding solvent.

ΔE_{int} was set equal to $\Delta <\psi|H|\psi>$ from continuum solvent calculations (and considering E2 energy corrections in MP2 calculations), and the corrected $\Delta E_{int} = \Delta E_{int}(corr)$ was calculated at the QCISD(T) level as

$$\Delta E_{int}(corr) = \Delta <\psi|H|\psi> + (\Delta E(IEF−PCM/QCISD(T)) − \Delta <\psi|H + 1/2V|\psi>) \quad (3)$$

The QCISD(T) calculations[11] were performed at the previously optimized geometry using the 6-31G(d) basis set.

Thermal corrections at the IEF−PCM/B3LYP/6-31G(d,p) level for obtaining relative internal free energies for the species at $T = 298$ K and $p = 1$ atm in the rigid rotator, harmonic oscillator approximation[21] were calculated as

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$$\Delta G_{\text{thermal}} (T) = \Delta ZPE + \Delta(H(T) - ZPE) - T\Delta S(T) \tag{4}$$

where ZPE stands for the zero-point energy. Since the experimental tautomerization constants K_T were defined as[5]

$$K_T = [\text{quinone}]/[\text{phenol}] \tag{5}$$

all relative quantities ΔX described above are obtained as the difference between the respective values for 1HK and 1HA, $\Delta X = X(1HK) - X(1HA)$.

To correct for some shortcomings of the MP2 procedure, Grimme has suggested a modified version, spin-component-scaled MP2 (SCS-MP2)[27a] on the basis of a different scaling of the spin-parallel and spin-antiparallel electron pair contribution to the correlation energy, $E_c = p_S E_S + p_T E_T$. With this correction scheme, indeed a significant improvement of MP2 energies, comparable to those from the much more expensive QCISD-(T) calculations, can be obtained.[27] Consequently, this method also has been used here. For the scaling factors, the values derived in the original paper,[27a] $p_S = ^6/_5$ and $p_T = ^1/_3$, were used.

The experimental tautomerization constants K_T were obtained[5a] by a chemometric[28] analysis of the UV/vis spectra of the tautomeric mixture in the respective solvent.

Results and Discussion

Relative Free Energies. The equilibrium outlined in Scheme 1 shows sensitive solvent effects. Fabian et al. pointed out experimentally[5a] that the imine−enol form is more stable than the amine−quinone structure by 1.96 kcal/mol in the gas phase. In aqueous solution, however, the quinone−amine tautomer is preferred by 0.67 kcal/mol. In several organic solvents, the equilibrium is subtle, and decrease of the solvent polarity gradually increases the imine−enol form, which is the more stable one in the gas phase.[5a] In our present study, we chose two medium-polarity solvents, methanol and acetonitrile, with different hydrogen-bond formation capacity, and an apolar but readily polarizable solvent, carbon tetrachloride.

The results from the IEF−PCM calculations are summarized in Table 1. The general conclusion regarding the B3LYP method is that the calculated ΔG_{tot} values are too negative compared to the experimental ones. The (absolute) B3LYP/ΔE_{int} values vary within a 0.6 kcal/mol range, whereas ΔE_{int} increases to 4−6 kcal/mol when the MP2/6-31G(d,p) method is used. As a result, the calculated ΔG_{tot} values become strongly positive in comparison with the experiment.

To rationalize observed solvent effects in iminoenol−aminoketon or azo−hydrazo tautomerism, frequently specific solvent effects have been postulated,[5b,29] and besides continuum solvation models, solute−solvent complexes were considered in the calculation of tautomerization constants.[5b,30] Generally, thereby at least trends were more satisfactorily reproduced, even by quite low-level calculations. Use of the supermolecule-continuum solvation approach may be even more important in conformational analysis. To obtain good results for the conformer population for the zwitterionic γ-amino butyric acid in aqueous solution, Crittenden et al.[31] surrounded the solute by up to five explicit water molecules, and this supermolecule was placed into the cavity carved in the continuum. In the absence of periodic boundary conditions, however, water association instead of solute solvation at all polar sites may appear. Furthermore, the larger the solute, the larger number of explicit solvent molecules are needed for an unambiguous solvation, and even when a medium-size basis set has been applied, serious
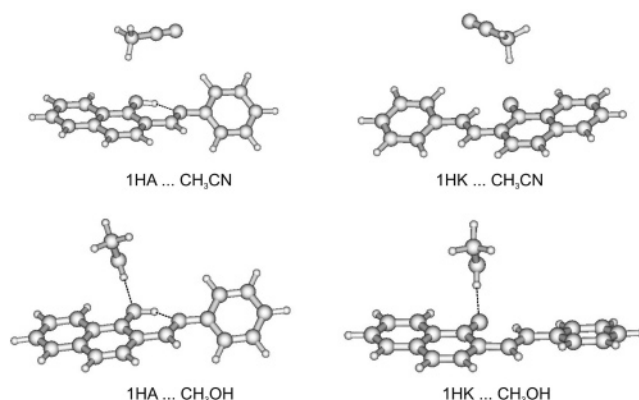

Figure 1. Calculated [IEFPCM-B3LYP/6-31G(d,p)] structures of complexes 1HA/1HK with one molecule of acetonitrile or methanol in the respective solvent.

TABLE 1: Free Energies of the Quinone Form Relative to the Enol Form from Continuum Calculations[a]

IEF-PCM	CH₃OH	CH₃CN	CCl₄
	B3LYP/6-31G(d,p)		
ΔE_{int}	0.60	0.60	-0.15
$\Delta\langle\psi|1/2V|\psi\rangle$	−3.20	−3.15	−1.00
ΔG_{drc}[b]	−0.10	−0.09	−0.10
ΔG_{therm}[b]	−0.50	−0.36	−0.38
ΔG_{tot}	−3.20	−3.00	−1.63
	B3LYP/6-311++G(d,p)[c]		
ΔE_{int}	0.54	0.55	−0.34
$\Delta\langle\psi|1/2V|\psi\rangle$	−3.79	−3.72	−1.15
ΔG_{tot}	−3.85	−3.62	−1.97
	MP2/6-31G(d,p)[c]		
ΔE_{int}	6.02	6.04	4.27
$\Delta\langle\psi|1/2V|\psi\rangle$	−4.12	−4.06	−1.30
ΔG_{tot}	1.30	1.53	2.49
	MP2/6-311++G(d,p)[c]		
ΔE_{int}	7.79	7.82	5.72
$\Delta\langle\psi|1/2V|\psi\rangle$	−4.58	−4.52	−1.41
ΔG_{tot}	2.61	2.85	3.83
	(1.61)	(1.45)	(2.91)
ΔG_{exp}	−0.09	−0.13	0.97

[a] Relative energy components in kcal/mol (a negative sign indicates greater stability of the quinone tautomers 1HK). [b] Both ΔG_{drc} and ΔG_{therm} were accepted as unaltered in single-point energy calculations. [c] Single-point calculations at the IEF−PCM/B3LYP/6-31G(d,p) optimized geometry; SCS-MP2 results are given in parentheses.

convergence problems may emerge throughout the IEF−PCM geometry optimization.

In the present case with an intramolecular proton jump, consideration of an explicit solvent molecule in a solute complex (1HA/1HK + CH₃OH and 1HA/1HK + CH₃CN, Figure 1) does not significantly alter the results: ΔG_{tot} is −3.1 and −2.3 kcal/mol in methanol and acetonitrile, respectively, at the IEF−PCM/B3LYP/6-31G(d,p) level. Both the 1HA + CH₃OH and 1HK + CH₃OH complexes are characterized by an intermolecular CH₃OH⋯O hydrogen bond involving the hydroxy (1HA) and keto (1HK) oxygen atom. The computed structures of the 1HA + CH₃CN or the 1HK + CH₃CN complexes barely seem to indicate the presence of intermolecular hydrogen bonds. Possibly, in 1HA weak hydrogen bonds between a methyl hydrogen of CH₃CN and the OH oxygen and also an aryl hydrogen and the nitrile nitrogen atom exist; in the 1HK + CH₃CN complex only a NC−CH₂H⋯O hydrogen bond to the quinine oxygen atom could be present. A rotamer of 1HA capable of forming an intermolecular O−H⋯O hydrogen bond to the methanol

TABLE 2: Free Energies of the Quinone Form Relative to the Enol Form with IEF−PCM/QCISD(T)/6-31G(d)//IEF−PCM/ B3LYP/6-31G(d,p) Internal Energies and with FEP/MC Solvation Free Energies[a]

	CH$_3$OH		CH$_3$CN		CCl$_4$
	CHELPG	RESP	CHELPG	RESP	CHELPG
ΔE_{int} (corr)	3.21		3.21		1.80
ΔG(solv)	-3.33 ± 0.08^b	-3.25 ± 0.08	-2.95 ± 0.07^b	-2.12 ± 0.07	-0.17 ± 0.06
	-3.46 ± 0.08^b		-2.90 ± 0.08^b		
			-3.17 ± 0.12^c		
ΔG_{therm}	-0.50		-0.36		-0.38
ΔG_{tot}	-0.69^d		-0.08^d		1.25
ΔG_{exp}	-0.09		-0.13		0.97

^{a} Energies in kcal/mol. ^{b} Top and bottom values calculated from the 1HA to 1HK forward and backward simulations, respectively. ^{c} By explicit consideration of a CH$_3$CN molecule in optimized position. ^{d} Calculated by using the average of the forward and backward ΔG(solv) values.

oxygen atom is significantly higher in energy, $\Delta G_{tot} = +7.6$ kcal mol^{-1}. An analogous isomer of the 1HA + CH$_3$CN complex with an O−H···N≡C−CH$_3$ arrangement is also quite high in energy, $\Delta G_{tot} = +9.3$ kcal/mol. Thus, only the conformers indicated in Scheme 1 have been further studied.

Basis set effects were considered by performing IEF−PCM/ B3LYP/6-311++G(d,p) and IEF−PCM/MP2/6-311++G(d,p) single-point calculations. Since the geometry was set to the one optimized at the IEF−PCM/B3LYP/6-31G(d,p) level, deviations in the corresponding energy terms are only due to the larger basis set using either the B3LYP or the MP2 method. Although ΔE_{int} changes only slightly upon basis set extension at the B3LYP level, the $\Delta <\psi|1/2V|\psi>$ term becomes more negative and the B3LYP/6-311++G(d,p) single-point calculations even more overestimate the stability of the 1HK quinone tautomer than with the lower basis set. In contrast, MP2/6-311++G(d,p) calculations predict increases for all relative internal energy terms, and the resulting more positive ΔG_{tot} values characterize equilibria shifted always toward the 1HA enol instead of the 1HK quinone form with negative or less positive (carbon tetrachoride solvent) experimental ΔG_{tot} values in Table 1. Correcting the MP2 correlation energy by separately scaling the spin-parallel and spin-antiparallel components according to the proposal of Grimme (SCS-MP2)[27] significantly reduces the difference between experimental and calculated K_T values (Table 1), although the difference still remains too large. However, the experimental values for the tautomerization constants depend on the methods used for their determination. For instance, K_T values obtained by a chemometric analysis of UV/vis spectra of the isomeric 2-hydroxy-1-naphthaldehydethe anil, 2HA−2HK (Scheme 1), in CHCl$_3$ and CH$_3$CN, respectively, are 0.52 and 0.56.[5b] In contrast, ^{13}C NMR spectroscopy leads to $K_T = 1.83$ (CHCl$_3$) and $K_T = 1.50$ (CH$_3$CN).[29a] For the 1HA−1HK tautomeric equilibrium, this latter method gives $K_T = 0.95$ and $\Delta G_T = +0.03$ kcal mol^{-1} in chloroform.[29c]

Our theoretical results allow the conclusion that the poor estimate of ΔG_{tot} by the IEF−PCM method at the B3LYP or the MP2 levels is primarily due to the inadequate prediction of the relative internal energy because of correlation effects.[8,9] The larger basis set does not improve the results. These experiences suggest that relative internal energies should be calculated at a high level rather than with a large basis set. Thus, single-point IEF−PCM/QCISD(T) calculations, as high-level electron-correlation calculations, were performed with the affordable 6-31G-(d) basis set.

The calculated ΔE_{int} values are provided in Table 2. The values are about halfway between the B3LYP and MP2 relative internal energies in Table 1. Considering these ΔE_{int} values in combination with the FEP/MC ΔG(solv) values in eq 1, the calculated ΔG_{tot} values dramatically improve. They are in very

good and good agreement with the experimental ΔG_{tot} in acetonitrile and carbon tetrachloride, respectively, whereas the relative total free energy is too negative by 0.6 kcal/mol in methanol. The better agreement is primarily attributed to the improvement of the ΔE_{int} term. Concerning the results obtained for methanol solution, the experimental value might be to some extent an "outlier": for ethanol,[5a] which is not expected to be too different, $\Delta G_{exp} = -0.24$ kcal/mol. Relative solvation free energies from the continuum approach (eq 2b) were calculated at -3.30, -3.24, and -1.10 kcal/mol at the IEF−PCM/B3LYP/ 6-31G(d,p) level (Table 1) compared to the corresponding FEP/ MC values of -3.40, -2.93, and -0.17 kcal/mol in methanol, acetonitrile, and carbon tetrachloride, respectively (Table 2). Thus, the ΔG(solv) values are close in the two polar solvents and differ by about 1 kcal/mol in the apolar carbon tetrachloride. The smaller or larger differences in ΔG(solv) do not account, however, for the improvement in ΔG_{tot}, which can be primarily attributed to the ΔE_{int} term calculated at the IEF−PCM/QCISD-(T)/6-31G(d) level.

Atomic Charge Sets. Another goal of the present investigations was to compare different atomic charge sets used in the FEP/MC calculations. Since the solvent affects the solute charges, solvent-dependent, effective in-solution charges are consistent with the applied energy terms in eq 1. Derived charges for the three polar atoms are compared in Table 3.

The atomic charges show small solvent and remarkable derivation-method dependence. N, O, and H atomic charges in the enol form hardly differ in different solvents according to the CHELPG derivation. Charges in the quinone form are more solvent-dependent: the atomic charges change in the ranges of -0.434 to -0.469, -0.576 to -0.620, and 0.358 to 0.368.

When the RESP derivation was applied, much smaller atomic charges were obtained in absolute value. The nitrogen charges are less negative by 0.3−0.4 atomic units than obtained with the CHELPG method. Differences in the oxygen and hydrogen charges are also about 0.1 units with the two methods. These are very large differences and raise two questions. Could both sets be reliable, and which set provides the ΔG(solv) values that allow an estimate of ΔG_{tot} close to the experimental one?

A possible test for the charge reliability is the predicted dipole moment. Although we do not have experimental values for the present structures, some qualitative expectations may be outlined. In a theoretical study for small organic molecules, the PCM method predicted an increase of the dipole moments by up to 30% in aqueous solution compared to the gas-phase values.[32] The dipole moment of 4-pyridone (subject to tautomerization to 4-OH pyridine, similar to a quinone−enol tautomerization) was reported as 6.0−6.3 D in dioxane[33a,b] and was calculated as 9.4−11.1 D in aqueous solution at the IEF−PCM/B3LYP level using the 6-31G* and 6-311++G** basis

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TABLE 3: Dipole Moments[d] and Polar-Atom Charges in Solution

DM(gas)[a]				
enol	1.60			
quinone	2.76			

	CH$_3$OH		CH$_3$CN		CCl$_4$
DM(sol)[b]					
enol	2.65		2.65		1.96
quinone	4.58		4.58		3.46
ϵ	32.63		36.64		2.23

	CHELPG	RESP	CHELPG	RESP	CHELPG
DM(ELPO)[c]					
enol	2.66	2.65	2.66	2.63	1.98
quinone	4.58	4.57	4.58	4.58	3.46
atomic charges					
enol					
N	−0.518	−0.200	−0.506	−0.158	−0.510
O	−0.548	−0.426	−0.543	−0.431	−0.524
H	0.387	0.262	0.382	0.252	0.380
quinone					
N	−0.434	−0.079	−0.469	−0.127	−0.442
O	−0.614	−0.536	−0.620	−0.528	−0.576
H	0.364	0.243	0.368	0.245	0.358

[a] B3LYP/6-31G(d,p) values. [b] IEF−PCM/B3LYP/6-31G(d,p) values calculated at the ϵ dielectric constant as indicated. [c] Calculated from ELPO-fitted atomic charges using the CHELPG and the RESP procedure (see text). [d] Dipole moments (DM) in Debye.

sets.[33c] Thus, for this highly polar molecule, the dipole moment increases with the increasing polarity of the solvent. Sagnes and Casadevall[34] found that the dipole moments of alcohols and monofunctional organic acids in nonpolar solvents depend on the water content of the solvent, but the dipole moments of organic compounds containing CO, trivalent N, NO$_2$ functional groups, and halogens are practically constant in solvents with water content no more than 0.2 g/L in benzene and cyclohexane. A conspicuously small increase of the dipole moment in aqueous solution for trimethylamine, a representative of compounds with trivalent nitrogens, was also found in the theoretical study.[32]

Thus, the increasing polarity of the solvent may or may not increase remarkably the dipole moment of the solute. An interesting system is cyclohexanone (also subject to keto−enol tautomerization[35]), where the solvent environment decreases the dipole moment. The gas-phase value is 3.25 D, whereas the dipole moment for the neat liquid with a dielectric constant of $\epsilon = 16.1$ is 2.87 D,[36a] and the reported values are 3.08, 3.14, and 3.04 D in benzene, carbon tetrachloride, and cyclohexane, respectively.[36b]

The present quinone−enol tautomeric system may be characterized as behaving "regularly", meaning that the in-solution dipole moment, compared to the gas-phase value, gradually increases with increasing dielectric constant for the solvent. The dipole moments change by 1.5−2.0 D upon the tautomeric change. In agreement with related tautomeric pairs,[29a,30] the calculated dipole moments for the quinone forms are larger than for iminoenol (azo) tautomers. The obtained values are very similar in methanol and acetonitrile solutions. The reason is that the dielectric constants for these solvents are similar, 32.63 and 36.64, as taken from the default parameter set of the Gaussian 03 implementation. With the remarkably lower value of $\epsilon = 2.23$ for carbon tetrachloride, the calculated dipole moments are smaller, showing smaller polarization of the solutes. Since despite the different atomic charges, both the CHELPG and RESP sets reproduce very well the IEF−PCM/B3LYP/6-31G-(d,p) dipole moments in all five cases in Table 3, the charges

themselves do not provide a basis for selecting a preferred charge-derivation method.

Table 2 shows that the ΔG(solv) values are also very similar with the two solute charge sets in methanol. Forward and backward simulations with the CHELPG set indicate that the difference in the two FEP/MC calculations is in the order of the magnitude of the standard deviation. Thus, our calculations are robust at the selected simulation parameters, both in methanol and acetonitrile. In acetonitrile, however, prediction of good ΔG_{tot} was possible only by means of the ΔG(solv)/ CHELPG value. Then, only this parametrization was applied in carbon tetrachloride solvent, where small relative solvation free energy was expected. The dispersion interaction, proportional to r^{-6} in the OPLS-12−6−1 all-atom force field, must be nearly equally favorable for both tautomers. The electrostatic component of the ΔG(solv) should be small because of the nonpolar character of the solvent. The calculation results confirmed the expectations: the Coulomb and Lennard-Jones (12−6) solute−solvent interaction energies are −0.05 ± 0.02 and −36.03 ± 0.19 kcal/mol for the imine−enol and −0.03 ± 0.02 and −36.09 ± 0.18 kcal/mol for the quinone−amine tautomer, respectively, in carbon tetrachloride.

Dipole moments, or more precisely the difference in the dipole moments between the two tautomeric forms together with structural differences (twist angle of the phenyl ring), have been used to estimate the entropic contribution, $-T\Delta S$, to the enol imine ↔ enaminone reaction in substituted salicylidene anils.[30] Obviously, for such an analysis to be statistically meaningful, a series of compounds would be necessary. Information about the azo−hydrazo tautomerism in the analogous 4-phenylazo-1-naphthol and 1-phenylazo-2-naphthol has been obtained by comparison of the experimental dipole moments with those calculated for the individual tautomeric species.[37] The dipole moments of the isomeric 2-hydroxy-1-naphthaldehyd anil 2HA− 2HK and substituted derivatives thereof have been determined in dioxane ($\mu = 2.88$ D[38a] and 2.39 D[38b]) and benzene ($\mu = 2.18$ D[38a]), however, without reference to a specific tautomeric form. Instead, assuming a structure averaged over the phenol and quinine tautomer, by comparison of experimental polarizabilities with those estimated from group contributions, the twist angle of the substituted aniline ring was estimated.[38b]

Conclusions

The tautomeric equilibrium (phenol−quinone, iminoenol− enaminone) of the 1-hydroxy-2-naphthaldehyde Schiff base (2-phenyliminomethyl-naphthalen-1-ol), 1HA/1HK, was investigated by density functional theory (B3LYP) and ab initio (MP2) methods in the IEF−PCM polarizable continuum dielectric solvent approximation. Special emphasis was put on the effect of solvation on this equilibrium by using an apolar (CCl$_4$), polar aprotic (CH$_3$CN), and polar protic (CH$_3$OH) solvent. On the basis of IEF−PCM/B3LYP/6-31G(d,p) geometries, relative solvation free energies were obtained by Monte Carlo free-energy perturbation simulations.

Compared with experimental tautomerization Gibbs free energies, the B3LYP calculations apparently overestimate the stability of the quinone form, 1HK, whereas with MP2 the aromatic phenol tautomer, 1HA, has been found to be considerably too stable. Results are not qualitatively different when calculated with the 6-31G(d,p) or the 6-311++G(d,p) basis sets. A significant improvement between calculated and experimental ΔG_{tot} values can be obtained by calculating ΔE_{int} with IEF− PCM/QCISD(T)/6-31G(d) level correlation contribution. When the total relative in-solution free energy was calculated as ΔG_{tot}

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$= \Delta E_{int}(\text{IEF}-\text{PCM/QCISD(T)/6-31G(d)}) + \Delta G(\text{solv, MC}) + \Delta G_{thermal}$, the ΔG_{tot} values agreed with the experimental ones up to 0.6 kcal/mol, and the predominant tautomer was always correctly predicted.

In-solution relevant atomic charges, derived by fitting to the molecular electrostatic potential generated by the IEF−PCM/B3LYP/6-31G(d,p) wave function, show strong dependence on the fitting procedure (CHELPG and RESP) and are fairly insensitive to the chemical nature of the actual solvent. Use of the CHELPG charges in calculating $\Delta G(\text{solv, MC})$ revealed to be superior in comparison with applying RESP charges.

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