# Structure of Charged Cyclohexyldiamines in Aqueous Solution: A Theoretical and Experimental Study

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**S** *Supporting Information*

**ABSTRACT:** The structure of mono- and diprotonated cyclohexyldiamine isomers in aqueous solution is investigated theoretically by the application of the CPCM continuum solvation model combined with the MP2/aug-cc-pVDZ model chemistry. The calculated Gibbs energy of hydration ($\Delta G_{hyd}$) is expressed in different terms with physical meaning: cavity formation, solute conformational variation, and solute–solvent interaction. Significant differences of the $\Delta G_{hyd}$ values are found among isomers, which are interpreted based on the analysis of the factors accounting for the stability of the conformers/isomers in the gas and solution phases. Particular attention is given to the role played by the formation of an intramolecular hydrogen bond in the monoprotonated forms and by the Coulombic repulsion between the $NH_3^+$ groups in the diprotonated ones. From the Gibbs energies of the acid/base pairs in the gas phase and respective hydration Gibbs energies, the acidity constants ($pK_a$) are calculated and interpreted. For some isomers, the constants are also determined experimentally by potentiometric titration. A good agreement was found between the calculated and experimental values.
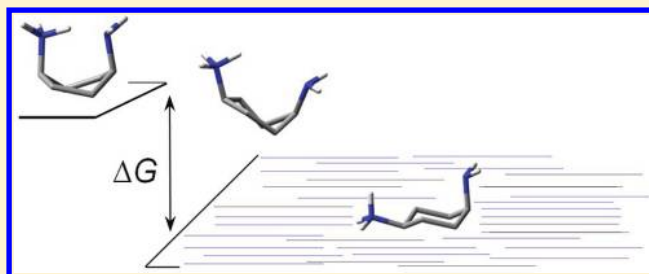
## 1. INTRODUCTION

The amino group is present in many compounds ubiquitous in nature, playing an important role in their molecular structure and chemical behavior.[1] In aqueous solution, depending on the pH, it may be in the acid ($-NH_3^+$) or basic ($-NH_2$) form and can participate in intra- and/or intermolecular interactions as ionic or dipolar group.

The structure of simple charged monoamines in aqueous solution has been studied experimentally[2−4] and theoretically.[5−8] Conversely, just a few works have been published on charged diamines.[9−11] The study of these molecules assumes particular importance since many compounds of biological and industrial interest are polyamines in which the mutual interactions between the amino groups may significantly influence their properties.

The present work is dedicated to the study of the structure of mono- and diprotonated cyclohexyldiamine isomers in aqueous solution and their acid–base properties. This study is based on the data obtained for the Gibbs energy corresponding to the gas–solution transfer process (solvation). Besides their own interest, the systems under investigation provide valuable information on the hydration of polyamines. In fact, we can learn about the effect of the distance between a charged and an uncharged amino group, or between two charged groups, as well as the influence of their equatorial or axial configuration relative to the cyclohexyl ring. From here on, the unprotonated, monoprotonated, and diprotonated cyclohexyldiamines are designated as CHDA, CHDA$^+$, and CHDA$^{2+}$, respectively.

The Gibbs energies of hydration of the molecules are computed by applying the conductor-like polarizable continuum model (CPCM)[12] and the MP2/aug-cc-pVDZ model chemistry. This is quite an effective method to calculate a meaningful thermodynamic property for studying the structure of solutions that is difficult to determine experimentally for many chemical systems.

In the modern theories of thermodynamic interpretation of solvation, various physical components of the transfer process are taken into account.[13] Besides the classical components (cavity formation and solute–solvent interaction), the change of the solute conformation from that present in gas phase to that it acquires by interaction with the solvent should be taken into account. This term, which is often neglected, may affect the values of the Gibbs energy or enthalpy of solvation.[14,15]

The $pK_a$ values were estimated from the Gibbs energies of CHDA$^{2+}$, CHDA$^+$, and CHDA in the gas phase and their Gibbs energies of hydration. The data needed for the gas-phase calculations were published previously by the authors.[16,17] For some isomers the $pK_a$ values were also determined experimentally by potentiometric titration. The comparison of the values obtained by theoretical and experimental means are, to a certain extent, a test of the reliability of the methodology used in the calculation of the hydration Gibbs energies of the charged species.

## 2. THERMODYNAMICS BACKGROUND

In this work, the hydration Gibbs energy ($\Delta G_{hyd}$) is defined as the Gibbs energy variation corresponding to the transfer of the solute molecule from an ideal gas at 1 M concentration to a 1 M ideal dilute aqueous solution. Thus, it is given by

$$\Delta G_{hyd} = G_{sol} - G_{gas} \tag{1}$$

$G_{sol}$ and $G_{gas}$ are the Gibbs energies of the solute in the solution and gas phase, respectively. $\Delta G_{hyd}$ may be expressed as the sum of different contributions consisting of cavity formation inside the solvent, $\Delta G_{cav}$; conformational variation of the solute, $\Delta G_{conf}$; and solute−solvent interactions, $\Delta G_{s-S}$. For a given solute conformer i, $\Delta G_{hyd,i}$ can then be written as

$$\Delta G_{hyd,i} = \Delta G_{cav,i} + \Delta G_{conf,i} + \Delta G_{s-S,i} \tag{2}$$

In order to appreciate the nature of the solute−solvent forces, $\Delta G_{s-S}$ can be considered as resulting from the following types of interactions: electrostatic ($\Delta G_{elec}$), dispersive ($\Delta G_{disp}$), and repulsive ($\Delta G_{rep}$).[18−20] Thus, expression 2 can be rewritten as

$$\Delta G_{hyd,i} = \Delta G_{cav,i} + \Delta G_{conf,i} + \Delta G_{elec,i} + \Delta G_{disp,i}$$
$$+ \Delta G_{rep,i} \tag{3}$$

When more than one conformer accounts for the structure of the solute, the thermodynamic properties are calculated by the following expressions

$$\Delta G_{hyd} = \left( \sum_i x_{sol,i} G_{sol,i} + RT \sum_i x_{sol,i} \ln x_{sol,i} \right)$$
$$- \left( \sum_i x_{gas,i} G_{gas,i} + RT \sum_i x_{gas,i} \ln x_{gas,i} \right) \tag{4}$$

$$\Delta G_{conf} = \sum_i x_{sol,i} G_{int,i} - \sum_i x_{gas,i} G_{gas,i} \tag{5}$$

$$\Delta G_{elec} = \sum_i x_{sol,i} \Delta G_{elec,i}; \quad \Delta G_{disp} = \sum_i x_{sol,i} \Delta G_{disp,i};$$
$$\Delta G_{rep} = \sum_i x_{sol,i} \Delta G_{rep,i} \tag{6}$$

where $x_i$ represents the Boltzmann population of conformer i in gas ($x_{gas,i}$) or solution ($x_{sol,i}$) and $G_{int,i}$ the intrinsic Gibbs energy of the solute conformer in solution, i.e., the Gibbs energy of the solute with the conformation exhibited in solution but calculated with the gas-phase Hamiltonian. If the conformer geometry is retained in solution, $G_{int,i} = G_{gas,i}$.

The acidity constant ($K_a$) is related to the standard Gibbs energy of the deprotonation reaction in aqueous solution, $\Delta G^0_{sol,deprot}$. For a monoprotonated form, this property is given by

$$\Delta G^0_{sol,deprot}(CHDA^+)$$
$$= 2.303 RT\, pK_{a,1}$$
$$= G_{sol}(CHDA) + G_{sol}(H^+) - G_{sol}(CHDA^+) \tag{7}$$

Introducing eq 1 into eq 7, we have

$$\Delta G^0_{sol,deprot}(CHDA^+)$$
$$= G_{gas}(CHDA) - G_{gas}(CHDA^+) + \Delta G_{hyd}(CHDA)$$
$$- \Delta G_{hyd}(CHDA^+) + G_{sol}(H^+) \tag{8}$$

Denoting $\Delta G_{gas}$ as the difference between the Gibbs energy of the basic and acid forms and $\Delta(\Delta G_{hyd})$ as the difference between their Gibbs energies of hydration, eq 8 can take the following short form:

$$\Delta G^0_{deprot,sol}(CHDA^+) = \Delta G_{gas} + \Delta(\Delta G_{hyd}) + G_{sol}(H^+) \tag{9}$$

Identical expressions to eqs 7, 8, and 9 are obtained for the deprotonation of $CHDA^{2+}$ into $CHDA^+$ ($pK_{a,2}$).

## 3. COMPUTATIONS IN AQUEOUS SOLUTION AND PERFORMANCE OF THE CPCM MODEL

The molecules studied in this work are the cis (c) and trans (t) configurations of the 1,2-, 1,3-, and 1,4-cyclohexyldiamine, abbreviated as c12, t12, c13, t13, c14, and t14. Mono- and diprotonated species are denoted by using "+" and "2+" as superscript. All possible conformers of the protonated forms have been previously explored in vacuum and their energies calculated at the MP2/aug-cc-pVDZ level of theory. The results of these calculations were published by the authors elsewhere.[16] These optimized structures were used as starting geometries for the calculations in aqueous solution.

The hydration Gibbs energies were computed using the CPCM model[12,21−23] implemented in the Gaussian 03 program package[24] and the same model chemistry employed in the gas-phase computations. To work as reference, similar calculations have been performed for cyclohexylamine (CHA).

Single points on the gas-phase-optimized geometries and full geometry optimizations in solution were carried out for some selected conformations. Since no significant variations were found in their hydration Gibbs energies, we decided to perform single-point calculations because of the lower computational expense and the large number of conformations to be evaluated (a total of 90 considering both neutral and charged species). Tight SCF convergence criteria were used in all calculations. The dielectric constant of water at 298.15 K ($\varepsilon = 78.4$) was used to simulate the aqueous environment and the cavitation term was obtained from the Pierotti−Claverie formula.[25,26] All calculations were performed at 298.15 K.

Although the study of hydration of the neutral diamines is out of the scope of the present paper, their Gibbs energies of hydration are needed to calculate the deprotonation constants in solution. The energies of these forms have been previously calculated at the CPCM/B3LYP/aug-cc-pVDZ level and the results are given in the authors' prior paper.[15] However, for consistency reasons, they were recalculated at the same level used for the charged forms.

To test the reliability of the CPCM/MP2/aug-cc-pVDZ method in the prediction of the Gibbs energies of hydration of neutral and charged aminic compounds, calculations were performed for small-size alkylamines for which experimental data are available. The set of molecules used for this purpose were methylamine, ethylamine, propylamine, cyclohexylamine, and 1,2-ethanediamine. Since no experimental data was available for dicharged amines, the calculations could not be extended to these forms.

In view of the strong influence of the solute−solvent boundary and cavity representation in the computed hydration Gibbs energies,[18] the calculations were performed using different molecular surfaces and different sets of atomic radii available in Gaussian 03. The best agreement between the experimental and computed energies was achieved by

representing the solute–solvent boundary as the solvent excluding surface (SES) and using the UAHF (united atom for Hartree–Fock)[27] and Bondi[28] radii for the neutral and charged molecules, respectively. The values computed for the tested molecules are given in Table 1 together with those determined experimentally.

**Table 1. Comparison of the Calculated (CPCM/MP2/aug-cc-pVDZ) Gibbs Energies of Hydration (298.15 K) of Some Alkylamines with Those Quoted from Experimental Determination**

| molecule | theor | exptl |
|---|---|---|
| $CH_3NH_2$ | −20.46 | −19.08[a] |
| $CH_3CH_2NH_2$ | −20.58 | −18.83[a] |
| $CH_3CH_2CH_2NH_2$ | −17.76 | −18.37[a] |
| $CH_3CH_2CH_2CH_2NH_2$ | −17.11 | −17.95[a] |
| $C_6H_{11}NH_2$ | −21.36 | −21.34[a] |
| $NH_2CH_2CH_2NH_2$ | −39.94 | −40.67[a] |
| $CH_3NH_3^+$ | −328.59 | −320.08[b] |
| $CH_3CH_2NH_3^+$ | −308.17 | −305.43[b] |
| $CH_3CH_2CH_2NH_3^+$ | −297.73 | −299.16[b] |
| $CH_3CH_2CH_2CH_2NH_3^+$ | −290.34 | −296.64[b] |
| $C_6H_{11}NH_3^+$ | −271.15 | −280.33[a] |

[a]Taken from refs 42 and 43. [b]Taken from ref 44.

## 4. POTENTIOMETRIC DETERMINATION OF THE ACIDITY CONSTANTS

The acidity constants were experimentally determined for c12 and t14. Best-grade commercially available compounds supplied by Fluka were used without any further purification. The purity degree, confirmed by chromatography, was found to be greater than 98% for c12 and 99% for t14. The potentiometric titrations were conducted in a galvanic cell consisting of a glass electrode and an Ag/AgCl/sat-KCl reference electrode. The diamine to be titrated was converted to the acid form by previous acidification of the solution to pH ≈ 2 with HCl. The ionic strength was adjusted to 0.1 M by adding KCl. The stepwise addition of a standard NaOH solution was made from an automatic buret Metrohm Dosimatic 725. Each titration was preceded by a blank test. All experiments were performed in nitrogen atmosphere to avoid $CO_2$ contamination and the temperature was controlled at 25.0 ± 0.1 °C. The buret and the potentiometer were connected to a computer to control the titrant addition and data acquisition. The value of the standard electromotive force was determined with the program Glee,[29] and the equilibrium constants were calculated with Hyperquad 2000.[30]

## 5. RESULTS AND DISCUSSION

The Gibbs energies in gas phase ($G_{gas}$) and aqueous solution ($G_{sol}$), Boltzmann populations ($x_{gas,i}$ and $x_{sol,i}$), and hydration Gibbs energies ($\Delta G_{hyd}$), all at 298.15 K, of the CHDA$^+$ and

**Table 2. Calculated Gibbs Energies in Gas Phase ($G_{gas,i}$) and Aqueous Solution ($G_{sol,i}$), Boltzmann Populations ($x_{gas,i}$, $x_{sol,i}$), and Hydration Gibbs Energies ($\Delta G_{hyd,i}$) at 298.15 K for the CHDA$^+$ Conformers**

| molecule | $G_{gas,i}$/hartrees[c] | $x_{gas,i}$ | $G_{sol,i}$/hartrees | $x_{sol,i}$ | $\Delta G_{hyd,i}$/kJ mol$^{-1}$ |
|---|---|---|---|---|---|
| **c12$^+$** | | | | | |
| eq$^+$,ax-g''[a] | −345.7511674 | 0.4095 | −345.8450634 | 0.5323 | −246.52 |
| ax$^+$,eq-a[a] | −345.7515129 | 0.5905 | −345.8449413 | 0.4677 | −245.30 |
| **t12$^+$** | | | | | |
| eq$^+$,eq-g[a] | −345.7523977 | 1.0000 | −345.8475986 | 0.9803 | −249.95 |
| ax$^+$,ax-g | −345.7335698 | 0.0000 | −345.8430372 | 0.0078 | −287.41 |
| ax$^+$,ax-g' | −345.7360000 | 0.0000 | −345.8429596 | 0.0072 | −280.82 |
| ax$^+$,ax-a | −345.7372159 | 0.0000 | −345.8425497 | 0.0047 | −276.55 |
| **c13$^+$** | | | | | |
| eq$^+$,eq-a | −345.7388794 | 0.0000 | −345.8483105 | 0.3278 | −287.31 |
| eq$^+$,eq-g | −345.7365045 | 0.0000 | −345.8482696 | 0.3139 | −293.44 |
| eq$^+$,eq-g' | −345.7383821 | 0.0000 | −345.8482560 | 0.3094 | −288.47 |
| ax$^+$,ax-a[a] | −345.7581792 | 1.0000 | −345.8465130 | 0.0488 | −231.92 |
| **t13$^+$** | | | | | |
| ax$^+$,eq-a | −345.7371293 | 0.0054 | −345.8458375 | 0.2697 | −285.41 |
| ax$^+$,eq-g' | −345.7369546 | 0.0045 | −345.8455433 | 0.1975 | −285.10 |
| eq$^+$,ax-a | −345.7420562 | 0.9892 | −345.8455346 | 0.1957 | −271.68 |
| ax$^+$,eq-g | −345.7351771 | 0.0007 | −345.8455064 | 0.1899 | −289.67 |
| eq$^+$,ax-g' | −345.7344921 | 0.0003 | −345.8452656 | 0.1472 | −290.84 |
| **c14$^+$** | | | | | |
| ax$^+$,eq-g' | −345.7367425 | 0.0000 | −345.8468697 | 0.4549 | −289.14 |
| eq$^+$,ax-a | −345.7428512 | 0.0000 | −345.8464772 | 0.3002 | −272.07 |
| ax$^+$,eq-a | −345.7393975 | 0.0000 | −345.8462673 | 0.2403 | −280.59 |
| TB (ax+,eq-a)[a,b] | −345.7543039 | 1.0000 | −345.8425424 | 0.0046 | −231.67 |
| **t14$^+$** | | | | | |
| eq$^+$,eq-g' | −345.7378718 | 0.0659 | −345.8494301 | 0.5974 | −292.90 |
| eq$^+$,eq-a | −345.7386821 | 0.1554 | −345.8490425 | 0.3963 | −289.75 |
| ax$^+$,ax-g' | −345.7349770 | 0.0031 | −345.8449325 | 0.0051 | −288.69 |
| ax$^+$,ax-a | −345.7402002 | 0.7757 | −345.8436270 | 0.0013 | −271.55 |

[a]Intramolecularly H-bonded conformers. [b]Structure with the cyclohexyl ring assuming a twist-boat (TB) conformation. [c]Taken from ref 16.

**Table 3. Calculated Gibbs Energies in Gas Phase ($G_{gas,i}$) and Aqueous Solution ($G_{sol,i}$), Boltzmann Populations ($x_{i,gas}$, $x_{i,sol}$), and Hydration Gibbs Energies ($\Delta G_{hyd,i}$) at 298.15 K for the CHDA$^{2+}$ Conformers**

| molecule | $G_{gas,i}$/hartrees[a] | $x_{gas,i}$ | $G_{sol,i}$/hartrees | $x_{sol,i}$ | $\Delta G_{hyd,i}$/kJ mol$^{-1}$ |
|---|---|---|---|---|---|
| c12$^{2+}$ | | | | | |
| eq$^+$,ax$^+$ | −345.9346649 | | −346.2829195 | | −914.34 |
| t12$^{2+}$ | | | | | |
| eq$^+$,eq$^+$ | −345.9356261 | 0.0048 | −346.2851224 | 0.5745 | −917.60 |
| ax$^+$,ax$^+$ | −345.9406678 | 0.9952 | −346.2848391 | 0.4255 | −903.62 |
| c13$^{2+}$ | | | | | |
| eq$^+$,eq$^+$ | −345.9679944 | 1.0000 | −346.2970331 | 1.0000 | −863.89 |
| ax$^+$,ax$^+$ | −345.9451948 | 0.0000 | −346.2824415 | 0.0000 | −885.44 |
| t13$^{2+}$ | | | | | |
| eq$^+$,ax$^+$ | −345.9610109 | | −346.2928874 | | −871.34 |
| c14$^{2+}$ | | | | | |
| eq$^+$,ax$^+$ | −345.9680036 | | −346.2940913 | | −856.14 |
| t14$^{2+}$ | | | | | |
| eq$^+$,eq$^+$ | −345.976221 | 1.0000 | −346.2981665 | 0.9997 | −845.27 |
| ax$^+$,ax$^+$ | −345.962037 | 0.0000 | −346.2905039 | 0.0003 | −862.39 |

[a]Taken from ref 16.

**Table 4. Gibbs Energies of Hydration (Population-Weighted Mean Values) and Respective Components (kJ mol$^{-1}$) at 298.15 K for the CHDA$^+$ and CHDA$^{2+}$ Isomers[a]**

| | isomer | | | | | |
|---|---|---|---|---|---|---|
| Gibbs energy variation[a] | c12$^+$ | t12$^+$ | c13$^+$ | t13$^+$ | c14$^+$ | t14$^+$ |
| $\Delta G_{hyd}$ | −245.87 | −250.00 | −239.40 | −275.70 | −244.98 | −287.43 |
| $\Delta G_{cav}$ | 97.95 | 99.30 | 101.38 | 99.98 | 99.47 | 101.90 |
| $\Delta G_{conf}$ | 0.11 | 0.88 | 50.56 | 12.34 | 39.40 | 4.24 |
| $\Delta G_{s-S}$ | −343.89 | −349.89 | −388.27 | −384.26 | −381.16 | −393.50 |
| $\Delta G_{elec}$ | −272.85 | −278.69 | −316.76 | −313.15 | −310.08 | −321.87 |
| $\Delta G_{disp}$ | −81.42 | −81.62 | −82.02 | −81.54 | −81.49 | −82.16 |
| $\Delta G_{rep}$ | 10.38 | 10.42 | 10.51 | 10.43 | 10.41 | 10.53 |
| | isomer | | | | | |
| Gibbs energy variation[a] | c12$^{2+}$ | t12$^{2+}$ | c13$^{2+}$ | t13$^{2+}$ | c14$^{2+}$ | t14$^{2+}$ |
| $\Delta G_{hyd}$ | −914.34 | −905.73 | −863.89 | −871.34 | −856.14 | −845.27 |
| $\Delta G_{cav}$ | 102.59 | 103.28 | 104.81 | 104.31 | 105.06 | 104.81 |
| $\Delta G_{conf}$ | 0.00 | 7.54 | 0.00 | 0.00 | 0.00 | 0.01 |
| $\Delta G_{s-S}$ | −1016.93 | −1014.94 | −968.70 | −975.65 | −961.21 | −950.08 |
| $\Delta G_{elec}$ | −944.55 | −942.40 | −895.48 | −902.85 | −888.36 | −876.77 |
| $\Delta G_{disp}$ | −82.80 | −82.96 | −83.76 | −83.30 | −83.35 | −83.85 |
| $\Delta G_{rep}$ | 10.42 | 10.42 | 10.54 | 10.50 | 10.50 | 10.54 |

[a]Values calculated through eqs 4−6.

CHDA$^{2+}$ conformers are given in Tables 2 and 3, respectively. The conformers are labeled by the equatorial or axial configuration of the amino groups relative to the cyclohexyl ring, abbreviated as eq/eq$^+$ and ax/ax$^+$, where the superscript "+" stands for the charged group. Since in CHDA$^+$ the Lp−N−C−H dihedral angle can adopt different orientations, we used the letters $a$ (anti), $g$ (gauche+), and $g'$ (gauche−), to denote dihedrals of ∼180, 60, and −60°, respectively. For example, ax$^+$,eq-$g'$ refers to a conformation in which the charged amino group is axial while the neutral is equatorial and the value of the Lp−N−C−H is close to −60°. From the values of the thermodynamic quantities computed for the conformers, the population-weighted mean quantities for the various isomers were calculated through eqs 4−6. The results are shown in Table 4. The calculated properties for the neutral diamines are available as Supporting Information.

**5.1. Hydration of the Monoprotonated Cyclohexyldiamines.** The results presented in Table 2 for the monoprotonated cyclohexyldiamines show large negative values of $\Delta G_{hyd}$ and pronounced variations of this property among isomers. The first aspect would be expected for a solute molecule containing an ionic and a dipolar group in a polar solvent as water; the second may be ascribed to structural differences in gas and/or solution. The data quoted for $G_{gas}$ indicate that the structural differences in gas contribute significantly to the $\Delta G_{hyd}$ variations. Regarding the effect of the structural variations in solution, we have to wait for the analysis of the solution process. The molecular structure of the CHDA$^+$ isomers in gas and solution media, as well as its variation in the course of the phase transfer, are discussed later in this paper.

The values of the Boltzmann populations in the gas phase indicate that in most of the molecules under study the conformational composition is practically reduced to one conformer. This is particularly noted in t12$^+$, c13$^+$, and c14$^+$. Previous studies undertaken in our research group using

different theoretical approaches, namely the NBO and AIM theories, show that these three molecules and $c12^+$ are strongly stabilized by a charge-assisted $N^+$—$H$···$N$ intramolecular hydrogen bond (H-bond).[16,31] NBO indicates a large overlap between the lone pair of the nitrogen atom $Lp(N_1)$ and the antibonding $N_2$—H orbital, $\sigma^*(N_2$—$H)$. The values calculated for the second-order perturbation energies corresponding to the orbital overlap range from $-70$ ($t12^+$) to $-305$ kJ mol$^{-1}$ ($c14^+$). This means that the charge transfer represents a very important contribution to these H-bonds. The AIM theory applied to the same molecules gives evidence for the existence a bond critical point (BCP) whose values of the electron density and respective Laplacian fall into the criteria established by Popelier for the establishment of a H-bond.[32] Moreover, the negative values of the energy density at the BCP indicate that these charge-assisted H-bonds have an electrostatic and covalent character.[31]

As consequence of the H-bond stabilization, only the internally bonded conformers are populated in the gas phase. Although in $t13^+$ the configuration of the two groups prevents the establishment of an intramolecular H-bond, the high stability of the $eq^+$,$ax$-$a$ conformer ($x_{gas,i} = 0.99$) is due the favorable charge—dipole interaction.[16] In some aspects, the behavior of this isomer in the gas phase is identical to the H-bonded ones.

The values of $\Delta G_{cav}$ highlight that for these solutes the energy required to open the cavity into water represents 35—42% of $\Delta G_{hyd}$ and therefore it cannot be neglected when we intend to examine the structure of the solutes in aqueous solution from $\Delta G_{hyd}$. As the systems we are dealing with are isomers, this term is almost constant for all solute molecules (Table 4). However, for solutes with different sizes it affects not only the values of the global property but also the differences among them.

In Table 4 are given the values of $\Delta G_{conf}$ for the CHDA$^+$ isomers, and Figure 1 depicts their conformational composition in both gas and solution phases. For interpretational purposes,

the following three types of behaviors are manifested by the isomers concerning the conformational term. (1) The first is characterized by an identical conformational composition in both phases as exhibited by the vicinal isomers (amine groups bonded to vicinal carbon atoms) $c12^+$ and $t12^+$. That is, the intramolecular H-bonded conformers remain as the most abundant ones in aqueous solution. This is consistent with the results of ab initio calculations carried out on protonated ethylenediamine—(water)$_3$ complexes.[11,33] Thus, the values of $\Delta G_{conf}$ are very small (<1 kJ mol$^{-1}$). (2) The second includes $c13^+$ and $c14^+$. In both isomers, the population of the H-bonded conformer is greatly reduced in solution. Conversely, the free H-bonded conformers with a negligible weight in the gas phase become the most abundant ones in solution. As result, the values of $\Delta G_{conf}$ are quite large (39 and 51 kJ mol$^{-1}$ for $c14^+$ and $c13^+$, respectively). (3) The third type of behavior occurs with $t13^+$ and $t14^+$ whose conformers do not present an intramolecular H-bond. A much smaller, although significant, conformational change is manifested by a value of $\Delta G_{conf}$ falling between those calculated for the other two groups of isomers ($\Delta G_{conf} = 4$ kJ mol$^{-1}$ for $t14^+$ and 12 kJ mol$^{-1}$ for $t13^+$).

The term of eq 5 more closely related with the solution structure is, of course, $\Delta G_{s-S}$. From the analysis of the values computed for this quantity and respective components (see Table 4), three points are noted: the large difference between $\Delta G_{s-S}$ and $\Delta G_{hyd}$, indicating that this term cannot be used alone for the molecular interpretation of hydration; large variations of $\Delta G_{s-S}$ among isomers, indicating that the structural variations of the solute in solution also contribute to $\Delta G_{hyd}$; the predominance of the electrostatic nature in the solute—solvent interactions.

The electrostatic component, representing 80% of $\Delta G_{s-S}$, arises mainly from the interaction of the charged and neutral amino groups with water. Their relative weight on $\Delta G_{elec}$ may be estimated by comparing the values of this component obtained for the neutral and charged CHA. The value computed for the first is $-22.15$ kJ mol$^{-1}$ and for the second is $-293.35$ kJ mol$^{-1}$. This means that, although the interaction of the $NH_2$ group with water cannot be neglected, a much greater contribution comes from $NH_3^+$.

The comparison of $\Delta G_{s-S}$ among isomers leads to a clear discrimination between two sets of CHDA$^+$s: the first, constituted by the nonvicinal isomers, $\Delta G_{s-S}$ ranges from $-381$ ($c14^+$) to $-393$ kJ mol$^{-1}$ ($t14^+$) and the second, formed by the vicinal isomers, the values computed for this term are less negative: $-344$ and $-350$ kJ mol$^{-1}$ for $c12^+$ and $t12^+$, respectively. The difference between these two sets (~40 kJ mol$^{-1}$) is related to the persistence of the intramolecular H-bond in the hydrated vicinal isomers, which decreases the interaction of the amino groups with water.

Besides the intramolecular H-bond, other conformational features such as the configuration and orientation of the amino groups may also affect the solute—solvent interaction. The results tabled for the ($c13^+$,$t13^+$) and ($c14^+$,$t14^+$) pairs of isomers indicate that the diequatorial configuration favors the solute—solvent interaction relative to the equatorial—axial or diaxial ones. In the first pair, the conformational population in $c13^+$ is diequatorial whereas that in $t13^+$ is $ax^+$,eq or $eq^+$,ax. The weighted-mean value of $\Delta G_{s-S}$ calculated for the former is 4 kJ mol$^{-1}$ more negative than that calculated for the latter. In the second pair, the predominant diequatorial configuration in $t14^+$ gives rise to a $\Delta G_{s-S}$ decrease of 12 kJ mol$^{-1}$ relative to $c14^+$. Even within the H-bonded isomers ($c12^+$ and $t12^+$) the rule of
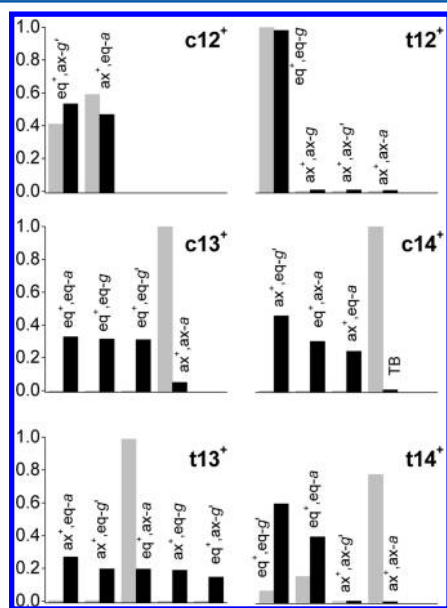


**Figure 1.** Boltzmann populations of the conformers of the monoprotonated CHDAs in gas phase (gray columns) and aqueous solution (black columns).

the stronger hydration of the diequatorial form is still valid. Indeed, $\Delta G_{s-S}$ of t12$^+$ is 6 kJ mol$^{-1}$ more negative than that of c12$^+$.

The stronger interaction of the polar substituents of cyclohexane equatorially oriented has been known for a long time.[34] It has also been observed for neutral cyclohexyldiamines in a previous authors' work.[15] An old interpretation to account for the effect of configuration on hydration is based on there being a better structural compatibility between the equatorial cyclohexane derivatives and the icelike structure assumed for the water.[34–37] In the work just referred to, the authors give arguments favoring an explanation based on a larger space available for the hydration sphere when the amino group is equatorial.

At the conformational level, the sequence of the $\Delta G_{hyd}$ values given in Table 2 shows that the solute−solvent interaction is also dependent on the orientation of the neutral amino group. Within each configuration, the $\pm gauche$ orientation of the Lp− N−C−H dihedral is more hydrated than the *anti*. Sometimes, this effect is even more pronounced than that resulting from the configuration. For example, the values of $\Delta G_{s-S}$ computed for c13$^+$(eq$^+$,eq-*a*), c13$^+$(eq$^+$,eq-*g*), and t13$^+$(ax$^+$,eq-*a*) are −388.6, −395.1, and −384.5 kJ mol$^{-1}$, respectively. The energy difference attributable to configuration is 4.1 kJ mol$^{-1}$ while that due to orientation is 6.5 kJ mol$^{-1}$. This finding is in agreement with the conclusions taken from the above-mentioned research on the hydration of the neutral forms.[15]

**5.2. Hydration of the Diprotonated Cyclohexyldiamines.** The cavitation, dispersion, and repulsion energies of the CHDA$^{2+}$ isomers are not significantly different from those of the monoprotonated forms. Regarding the conformational term, $\Delta G_{conf}$ is zero except for t12$^{2+}$ wherein the stability inversion from the diaxial into the diequatorial configuration gives rise to $\Delta G_{conf} = 7.5$ kJ mol$^{-1}$. Hence, the differences of $\Delta G_{hyd}$ among isomers are only related to differences in the solute−solvent interactions.

The values of $\Delta G_{hyd}$ are unexpected from the results found for the monoprotonated forms. Indeed, the structure of a CHDA$^{2+}$ may be regarded as resulting from the corresponding CHDA$^+$ by substituting the neutral amino group by a charged one. Hence, the difference of $\Delta G_{hyd}$ between the two forms were expected to be approximately that found between the charged and neutral CHA (−250 kJ mol$^{-1}$). Instead, the actual differences are 2.2−2.7 times greater than this figure. The increment of hydration of the diprotonated diamines relative to what would be expected if the charged groups behave independently is certainly due to the mutual interference between them. This effect becomes more pronounced as the distance between the groups decreases.

In Figure 2 are plotted the values of $G_{gas}$ and $G_{sol}$ as function of the distance between the nitrogen atoms. For graphical representation purposes, they are expressed relative to $G_{sol}$ calculated for t14$^{2+}$, the isomer with the furthermost amino groups. As shown in the figure, both quantities decrease linearly with distance, though with different slopes: −45.4 kJ mol$^{-1}$ Å$^{-1}$ in the gas phase, −17.3 kJ mol$^{-1}$ Å$^{-1}$ in solution. $\Delta G_{hyd}$, indicated by the vertical dotted lines, becomes more negative as the amino groups approximate each other. Although not represented in the figure, an identical variation with the N···N distance is found for $\Delta G_{s-S}$ and $\Delta G_{elec}$.

The results above prove that the deviations of $\Delta G_{hyd}$ relative to the values expected if the groups behave independently of one another, as well as the variation of $\Delta G_{hyd}$ with the N···N
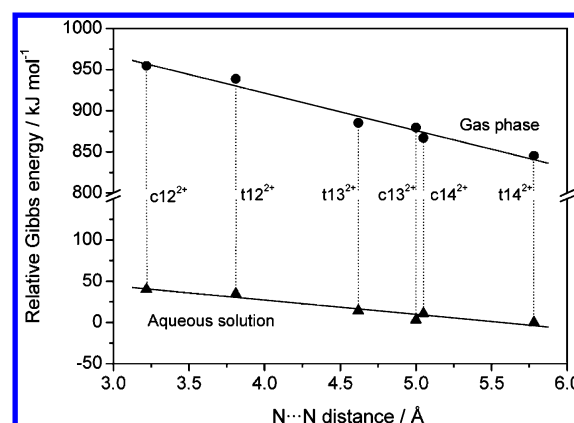


**Figure 2.** Variation of the Gibbs energy of the diprotonated diamines in gas phase (●) and aqueous solution (▲) with the distance between the nitrogen atoms. The Gibbs energy values were taken from Table 2 ($G_{gas}$ and $G_{sol}$) and are relative to the Gibbs energy of t14$^{2+}$ in aqueous solution. Solid lines represent the fitting curves.

distance, are due to the Coulombic repulsive forces between the two NH$_3^+$ charges. These interactions are responsible for the increase of the solute molecular energy in the gas state as the groups come closer together. An identical behavior occurs in solution, although attenuated relative to the gas phase. That is, the hydration of each group is influenced by the electric field of the other, becoming stronger as their distance decreases. The enhancement of hydration with the decrease of separation of charged amino groups has been experimentally observed by Kebarly et al. in doubly charged $\alpha,\omega$-alkanediamines produced in the gas phase by electrospray.[9,10]

**5.3. Acid/Base Properties.** In the discussion of acid/base reactions, eq 9 is that used for the simple reason that the decomposition of $\Delta G_{sol,deprot}$ into terms corresponding to the phenomena occurring in the gas phase and in solution allows a clear interpretation of the global process. The values of $G_{gas}$ of the protonated forms were calculated from the data given in Tables 2 and 3 for the conformers and those of $\Delta G_{hyd}$ were taken from Table 4. $G_{sol}(H^+) = -1122.49$ kJ mol$^{-1}$ was obtained from $G_{gas}(H^+) = -26.2836$ kJ mol$^{-1}$ [38] and $\Delta G_{hyd}(H^+) = -1096.21$ kJ mol$^{-1}$. The latter figure gives the best agreement between the theoretical and experimental p$K_a$'s and is quite close to that estimated by high-level ab initio calculations.[39]

The calculated p$K_a$ values are given in Table 5, together with those determined experimentally for c12 and t14. In this table

**Table 5. Experimental and Theoretical Acidity Constants in Aqueous Solution**

| molecule | p$K_{a,1}$ | | p$K_{a,2}$ | |
| | theor[a] | expt | theor[a] | expt |
|---|---|---|---|---|
| c12 | 8.86 | 9.59 | 5.56 | 6.18 |
|  |  | 9.93[b] |  | 6.13[b] |
| t12 | 8.68 | 9.94[b] | 5.91 | 6.47[b] |
| c13 | 9.28 |  | 10.35 |  |
| t13 | 9.07 |  | 9.50 |  |
| c14 | 8.92 |  | 9.80 |  |
| t14 | 9.20 | 9.15 | 10.62 | 9.31 |

[a] A statistical factor of log 2 was added to p$K_{a,1}$ and subtracted from p$K_{a,2}$ to account for the presence of two ionizable groups.[45,46] [b] Taken from refs 40 and 41.

**Table 6. Energy Differences between the Basic and Acid Forms Involved in the Deprotonation reactions**

| | $CHDA^+ \rightarrow CHDA$ | | | $CHDA^{2+} \rightarrow CHDA^+$ | | |
|---|---|---|---|---|---|---|
| isomer | $\Delta G_{gas}{}^{a,b}$ | $\Delta(\Delta G_{hyd})^{a,b}$ | $\Sigma^c$ | $\Delta G_{gas}{}^{a,b}$ | $\Delta(\Delta G_{hyd})^{a,b}$ | $\Sigma^c$ |
| c12 | 953.67 | 208.07 | 1161.74 | 481.24 | 668.47 | 1149.71 |
| t12 | 952.30 | 210.09 | 1162.39 | 494.24 | 655.73 | 1149.97 |
| c13 | 971.90 | 193.92 | 1165.82 | 550.87 | 624.49 | 1175.36 |
| t13 | 932.09 | 232.35 | 1164.44 | 575.01 | 595.64 | 1170.65 |
| c14 | 962.42 | 201.36 | 1163.78 | 561.07 | 611.16 | 1172.23 |
| t14 | 921.95 | 241.70 | 1163.65 | 620.74 | 557.84 | 1178.58 |

$^{a,b}$See eqs 8 and 9. $^c\Sigma = \Delta G_{gas} + \Delta(\Delta G_{hyd})$.

are further included the experimental $pK_a$'s of c12 and t12 published by other authors.[40,41] The reason for selecting c12 and t14 for the experimental determinations lies in the interest of having data about isomers with vicinal and remote amino groups.

An important conclusion drawn from the values shown in Table 5 is the agreement between the theoretical and experimental results. The differences between the results obtained by both procedures are in general lower than 0.8 $pK_a$ units, except for $pK_{a,1}$ of t12 and $pK_{a,2}$ of t14 wherein they are 1.3 $pK_a$ units. It is important to note the agreement and the theoretical coherence of the calculated results for the isomers and accordingly we stress its importance in both the reliability of the results and the computational method used.

The deprotonation consists of a substitution of one $NH_3{}^+$ by a $NH_2$ group. The unshared electron pair of the nitrogen atom gives to the last group a strong base character that leads to a very unfavorable gas-phase deprotonation. Furthermore, this process is rendered difficult by the strong interaction of the charged acid form with water. A favorable contribution to deprotonation comes from the strong hydration of the liberated proton. The strength of the acid depends on the balance of these three effects. In Table 6 are presented the values corresponding to the differences of the Gibbs energy in gas phase ($\Delta G_{gas}$) and of the Gibbs energy of hydration $[\Delta(\Delta G_{hyd})]$ between the basic and acid forms [see eq 9].

From this table, a great deal of information can be learnt concerning the acid/base properties of the diamines under study. For all isomers, the sum of $\Delta G_{gas}$ with $\Delta(\Delta G_{hyd})$ overcomes the absolute value of $G_{sol}(H^+)$. That is, all protonated forms are weak acids. Moreover, for the $CHDA^+$ deprotonation, $\Delta G_{gas} > \Delta(\Delta G_{hyd})$, meaning that the low acidity of the monoprotonated forms is mainly due to the basicity of the $NH_2$ group. Unlike for the $CHDA^{2+}$ deprotonation, although the difference between both terms is not as high as in the $CHDA^+$ deprotonation, $\Delta G_{gas} < \Delta(\Delta G_{hyd})$ except for t14$^{2+}$. Hence, the strong hydration of the diprotonated forms is the major reason for their low acidity.

Another interesting point to note based upon the data collected in Table 6 is the constant value of $\Sigma = [\Delta G_{gas} + \Delta(\Delta G_{hyd})]$ found for the $CHDA^+$ deprotonation, $\Sigma = 1163.6 \pm 1.5$ kJ mol$^{-1}$. The $\Delta G_{gas}$ variations, due fundamentally to the H-bond in $CHDA^+$, are accompanied by $\Delta G_{hyd}$ variations of the same amplitude but in opposite direction, making $\Sigma$ to remain constant. Therefore, all $CHDA^+$ isomers have an identical $pK_{a,1}$.

For the second deprotonation, the $CHDA^{2+}$ isomers with remote amine groups are different from the vicinal ones. While in the former, $\Sigma = 1174.2 \pm 3.5$ kJ mol$^{-1}$, making $pK_{a,2}$ to be slightly higher than $pK_{a,1}$, in the latter a much lower value is obtained, $\Sigma = 1150$ kJ mol$^{-1}$. This acidity increase results fundamentally from the repulsive effect between the $NH_3{}^+$

groups which is much more pronounced when they occupy vicinal positions.

With the $pK_a$ values, the variation of the mole fractions of the acid and base forms in solution with the pH can be calculated. This is depicted in Figure 3 for c12 and t14. The vicinal isomer
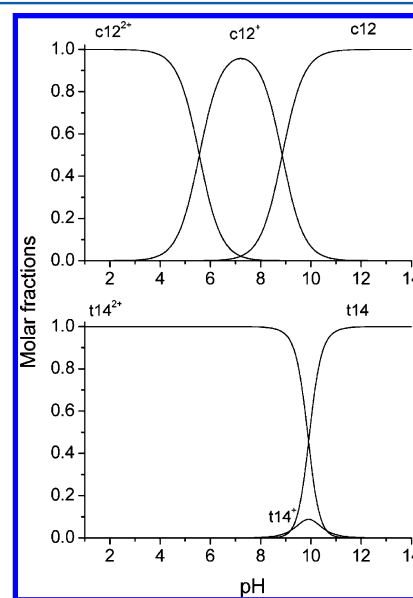


**Figure 3.** Distribution of the charged and neutral forms of c12 and t14 in aqueous solution as function of the pH. Molar fractions were calculated using the theoretical $pK_a$ values.

is diprotonated for pH < 3 and unprotonated form for pH > 11. Within these two pH values the monoprotonated form coexist with the other two, being practically the unique form presented in solution at the neutral pH. Regarding c14, the monoprotonated form is almost inexistent; its maximum molar fraction is 0.09 and is attained at pH = 10. For pH < 9 the compound is diprotonated and for pH > 11 only the neutral form exists.

## 6. CONCLUSIONS

The Gibbs energy of hydration of charged cyclohexyldiamines is made available for the first time. The calculations were performed at the CPCM/MP2/aug-cc-pVDZ level. The Gibbs energies of hydration of the isomers were taken as the population-weighted mean values computed for the conformers.

The Gibbs energy of hydration and related properties are consistent with the chemical structure of the molecules under consideration and, insofar as comparison is possible, they agree with the experimental data. The CPCM model has been object of intense research and has been successfully applied in the

computation of the Gibbs energy of hydration for neutral molecules. The results obtained in the present research demonstrate its applicability to charged solutes.

Because of the presence of one or two charged groups in the molecules under consideration, the electrostatic component of solute–solvent interaction is the major contribution to $\Delta G_{hyd}$. The conformational term, frequently neglected, also plays an important role in the hydration of some monoprotonated diamines, particularly in $c13^+$ and $c14^+$. Our results highlight the importance of this term and which on no account can be ignored in the calculation of $\Delta G_{hyd}$.

The intramolecular H-bond between the $NH_3^+$ and $NH_2$ groups is responsible for the variations of $\Delta G_{hyd}$ among the $CHDA^+$s. The isomers exhibiting this interaction in the gas phase are less hydrated. This behavior is explained by the weakening of the solute–solvent interaction when the H-bond persists in solution or by the large unfavorable conformational change. The structure and properties of the $CHDA^{2+}$ isomers are strongly affected by the Coulombic repulsion between the $NH_3^+$ groups. As these groups become closer it increases the molecular destabilization in the gas phase, but in aqueous solution it reinforces the interaction between the charged groups and water.

All protonated diamines are weak acids. The mean acidity constant calculated for the monoprotonated forms is $pK_{a,1} = 9.0 \pm 0.2$. Such small variation among isomers is explained by the compensation effect of the intramolecular H-bond in aqueous solution relative to the gas phase. Regarding the diprotonated diamines, the acidity constants of the vicinal isomers are approximately 4 $pK_a$ units lower than those of the nonvicinal isomers, $pK_{a,2} = 10.1 \pm 0.5$. The higher acidity of the formers is due to the strong electrostatic repulsion between the amino groups. As a consequence, at the physiological pH, the nonvicinal isomers are diprotonated while the vicinal ones are monoprotonated.

Despite the considerable number of quantities involved in the computation of the acidity constants, there is close agreement between the theoretical and experimental values. The $pK_{a,2}$ difference between the vicinal and nonvicinal isomers is confirmed by the results obtained from both methods.

## ■ ASSOCIATED CONTENT

### ⓢ Supporting Information

Results of the theoretical calculations (CPCM/MP2/aug-cc-pVDZ) performed for neutral cyclohexylamine and cyclohexyldiamines and complete ref 24. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes
The authors declare no competing financial interest.

## ■ REFERENCES

(1) *Amino Group Chemistry: From Synthesis to the Life Sciences*; Ricci, A., Ed.; Wiley-VCH: Weinheim, Germany, 2008.

(2) Perrin, C. L.; Gipe, R. K. *J. Am. Chem. Soc.* **1986**, *108*, 1088–1089.

(3) Perrin, C. L.; Gipe, R. K. *Science* **1987**, *238*, 1393–1394.

(4) Changa, H.-C.; Wangb, Y.-S.; Leea, Y. T.; Changa, H.-C. *Int. J. Mass Spectrom.* **1998**, *179/180*, 91–102.

(5) Intharathep, P.; Tongraar, A.; Sagarik, K. *J. Comput. Chem.* **2005**, *26*, 1329–1338.

(6) Jorgensen, W. L.; Gao, J. *J. Phys. Chem.* **1986**, *90*, 2174–2182.

(7) Filippo, B.; Marco, B.; Michele, P. *J. Chem. Phys.* **1999**, *110*, 4734–4736.

(8) Hesske, H.; Gloe, K. *J. Phys. Chem. A* **2007**, *111*, 9848–9853.

(9) Blades, A. T.; Klassen, J. S.; Kebarle, P. *J. Am. Chem. Soc.* **1996**, *118*, 12437–12442.

(10) Klassen, J. S.; Blades, A. T.; Kebarle, P. *J. Am. Chem. Soc.* **1994**, *116*, 12075–12076.

(11) Kim, K.-Y.; Chang, H.-C.; Lee, Y. T.; Cho, U.-I.; Boo, D. W. *J. Phys. Chem. A* **2003**, *107*, 5007–5013.

(12) Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. *J. Comput. Chem.* **2003**, *24*, 669–681.

(13) *Continuum Solvation Models in Chemical Physics: From Theory to Applications*; Mennucci, B., Cammi, R., Eds.; John Wiley & Sons: Chichester, UK, 2007.

(14) Lopes Jesus, A. J.; Tomé, L. I. N.; Eusébio, M. E. S.; Redinha, J. S. *J. Phys. Chem. B* **2006**, *110*, 9280–9285.

(15) Lopes Jesus, A. J.; Tomé, L. I. N.; Eusébio, M. E. S.; Rosado, M. T. S.; Redinha, J. S. *J. Phys. Chem.* **2007**, *111*, 3432–3437.

(16) Lopes Jesus, A.; Redinha, J. S. *Struct. Chem.* **2011**, *22*, 999–1006.

(17) Lopes Jesus, A. J.; Rosado, M. T. S.; Redinha, J. S. *Comput. Theor. Chem.* **2011**, *964*, 32–39.

(18) Takano, Y.; Houk, K. N. *J. Chem. Theory. Comput.* **2004**, *1*, 70–77.

(19) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027–2094.

(20) Tomasi, J.; Mennucci, B.; Cammi, R. *Chem. Rev.* **2005**, *105*, 2999–3094.

(21) Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995–2001.

(22) Klamt, A.; Schuurmann, G. *J. Chem. Soc., Perkin Trans. 2* **1993**, 799–805.

(23) Cossi, M.; Barone, V.; Cammi, R.; Tomasi, J. *Chem. Phys. Lett.* **1996**, *255*, 327–335.

(24) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; et al. *Gaussian 03, revision D.01*; Gaussian, Inc.: Wallingford, CT, 2004.

(25) Pierotti, R. A. *Chem. Rev.* **1976**, *76*, 717–726.

(26) Langlet, J.; Claverie, P.; Caillet, J.; Pullman, A. *J. Phys. Chem.* **1988**, *92*, 1617–1631.

(27) Barone, V. *J. Chem. Phys.* **1997**, *107*, 3210–3221.

(28) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441–451.

(29) Gans, P.; O'Sullivan, B. *Talanta* **2000**, *51*, 33–37.

(30) Gans, P.; Sabatini, A.; Vacca, A. *Talanta* **1996**, *43*, 1739–1753.

(31) Lopes Jesus, A. J.; Redinha, J. S. *J. Phys. Chem. A* **2011**, *115*, 14069–14077.

(32) Popelier, P. L. A. *Atoms in Molecules. An Introduction*; Prentice Hall: Harlow, UK, 2000.

(33) Boo, D. W. *Bull. Korean Chem. Soc.* **2001**, *22*, 693–698.

(34) Franks, F. *Water-A comprehensive treatise*; Plenum Press: New York, 1973; Vol. 2.

(35) Kabayama, M. A.; Patterson, D. *Can. J. Chem.* **1958**, *36*, 563–573.

(36) Kabayama, M. A.; Patterson, D.; Piche, L. *Can. J. Chem.* **1958**, *36*, 557–562.

(37) Warner, D. T. *Nature* **1962**, *196*, 1055–1058.

(38) Bartmess, J. E. *J. Phys. Chem.* **1994**, *98*, 6420–6424.

(39) Zhan, C.-G.; Dixon, D. A. *J. Phys. Chem. A* **2001**, *105*, 11534–11540.

(40) Serjeant, E. P.; Dempsey, B. *Ionization Constants of Organic Acids in Aqueous Solutions*; Pergamon: Oxford, UK, 1979.

(41) Perrin, C.; Dempsey, B.; Serjeant, E. P. *pK_a prediction of Organic Acids and Bases*; Chapman & Hall: London, 1981.

(42) Kelly, C. P.; Cramer, C. J.; Truhlar, D. G. *J. Chem. Theory. Comput.* **2005**, *1*, 1133–1152.

(43) Kelly, C. P.; Cramer, C. J.; Truhlar, D. G. *J. Phys. Chem. B* **2006**, *110*, 16066–16081.

5026

dx.doi.org/10.1021/jp3011712 | *J. Phys. Chem. B* 2012, 116, 5019–5027

(44) Pliego, J. R., Jr.; Riveros, J. M. *Phys. Chem. Chem. Phys.* **2002**, *4*, 1622−1627.

(45) Jang, Y. H.; Goddard, W. A.; Noyes, K. T.; Sowers, L. C.; Hwang, S.; Chung, D. S. *J. Phys. Chem. B* **2002**, *107*, 344−357.

(46) Bryantsev, V. S.; Diallo, M. S.; Goddard, W. A. *J. Phys. Chem. A* **2007**, *111*, 4422−4430.

**5027**

dx.doi.org/10.1021/jp3011712 | *J. Phys. Chem. B* 2012, 116, 5019−5027