Hydration of Cyclohexylamines: CPCM Calculation of Hydration Gibbs Energy of the Conformers

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This work presents a theoretical study on the hydration of cyclohexylamine and isomers of cyclohexyldiamine. All possible conformers were fully optimized in solution using the conductor-like polarizable continuum model (CPCM) and density functional theory. Values of the Gibbs energy of solvation, its respective contributions (electrostatic, nonelectrostatic and conformational change), and the relative Gibbs energy of the conformers in aqueous solution and gas phase are reported. From these values and the Boltzmann populations of the conformers in both phases, the weighted mean values of ΔG_{solv} for the compounds are calculated. Three structural features were found to be important for the hydration of these compounds: the distance between the two NH_2 groups (proximity disfavors hydration), their position relative to the ring (equatorial is preferred over axial), and the orientation of the nitrogen lone-pairs (gauche is more favorable to hydration than trans). In the particular case of vicinal cyclohexyldiamines, in addition to these two factors, the relative orientation of one group to the other should also be taken into account.

1. Introduction

The aim of the present paper is the investigation of the structure of cyclohexylamines in aqueous solution based on the solvation Gibbs energy. The compounds under study are cyclohexylamine (CHA) and cyclohexyldiamines (CHDA): *trans*-cyclohexyl-1,4-diamine (*trans*-1,4-CHDA), *cis*-cyclohexyl-1,3-diamine (*cis*-1,3-CHDA), *cis*-cyclohexyl-1,2-diamine (*cis*-1,2-CHDA), and *trans*-cyclohexyl-1,2-diamine (*trans*-1,2-CHDA).

The amine group is abundant in a variety of molecules of chemical and biological relevance. Furthermore, water is the most abundant liquid in nature and unique in biological media. The present work, dedicated to the study of aqueous solutions of amines, is therefore relevant to both the chemical and biochemical fields. The studied cyclohexylamines allow the simulation of the effect of a variety of solute molecular features on hydration, including the spatial orientation of the amine group, its position relative to the cyclohexane ring, together with the distance between the two functional groups. In spite of the relevance of these molecules, not much attention has been given to the study of their hydration, and as far as we are aware, only results on the hydration of small acyclic monoamines have been reported in literature.[1−3]

Recently, continuum solvation models have become attractive alternatives to the explicit approaches based on empirical potentials (molecular dynamics or Monte Carlo simulations), since they require less computational effort, making them applicable to larger molecules and also permitting the exploration of different conformations. Moreover, the possibility of combination of these models with ab initio or DFT electronic structure methods allows the treatment of the solute molecule at a high level of theory. Among the different solvation models available, the conductor-like polarizable continuum model (CPCM) is one of the most successful, and has proved to be very reliable in the prediction of the Gibbs energy of solvation of a great variety of neutral and charged organic molecules.[4−7]

In this work, the solvation Gibbs energies of the conformers of CHA and CHDA isomers were calculated by the CPCM continuum solvation model in combination with the highly successful B3LYP functional. In addition, taking the Gibbs energy values of the different conformers in both gas and aqueous solution, together with the respective mole fractions given by the Boltzmann populations, the values of the solvation Gibbs energy of each compound were determined.

2. Thermodynamic Formulation

The standard Gibbs energy of solvation (ΔG_{solv}), as used in this paper, is defined as the variation of this function in the following process:

$$\text{Solute (ideal gas, } C = 1\text{M)} \rightarrow \text{Solute (ideal dilute solution, } C = 1\text{M)} \quad (1)$$

$$\Delta G_{\text{solv}} = G_{\text{sol}} - G_{\text{gas}} \quad (2)$$

where G_{sol} and G_{gas} correspond to the molar Gibbs energy of the compound under consideration in solution and gas phase, respectively.

A thermodynamic property of solvation can provide a deeper insight into the structure of the compound if it is decomposed into terms with physical meaning which can be determined separately.[8] Hence, the Gibbs energy of the solute in solution can be considered as resulting from the sum of the following terms:
(i) The intrinsic Gibbs energy of the solute molecule in solution, i.e., a hard core molecule not interacting with the solvent, G_{int}; (ii) the energy required to create a cavity into the solvent to hold the solute molecule, ΔG_{cav}; (iii) the energy corresponding to the establishment of solute−solvent interactions, discriminat-

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ing the contributions coming from the Coulombic forces, ΔG_{elec}, London dispersive forces between the solute and the solvent, ΔG_{disp}, and the repulsive contribution between the solute and the solvent, ΔG_{rep}. The Gibbs energy of the solute in solution is, therefore, expressed as

$$G_{\mathrm{sol}} = G_{\mathrm{int}} + \Delta G_{\mathrm{cav}} + \Delta G_{\mathrm{elec}} + \Delta G_{\mathrm{disp}} + \Delta G_{\mathrm{rep}} \qquad (3)$$

The difference between G_{int} and G_{gas} corresponds to the variation of the solute molecular conformation accompanying the solvation process, ΔG_{conf}. Thus, we can write

$$\Delta G_{\mathrm{conf}} = G_{\mathrm{int}} - G_{\mathrm{gas}} \qquad (4)$$

From eqs 2 to 4, the Gibbs energy of solvation, corresponding to the solute−solvent coupling interaction in solution, is given by the following expression:

$$\Delta G_{\mathrm{solv}} = \Delta G_{\mathrm{conf}} + \Delta G_{\mathrm{cav}} + \Delta G_{\mathrm{elec}} + \Delta G_{\mathrm{disp}} + \Delta G_{\mathrm{rep}} \qquad (5)$$

The values of G_{sol} and G_{gas} for each compound can be considered as the weighted average of the values obtained for the respective conformers and calculated by the following equations:

$$G_{\mathrm{sol}} = \sum_{\mathrm{i}} x_{i,\mathrm{sol}} G_{i,\mathrm{sol}} + RT \sum_{\mathrm{i}} x_{i,\mathrm{sol}} \ln x_{i,\mathrm{sol}} \qquad (6)$$

$$G_{\mathrm{gas}} = \sum_{\mathrm{i}} x_{i,\mathrm{gas}} G_{i,\mathrm{gas}} + RT \sum_{\mathrm{i}} x_{i,\mathrm{gas}} \ln x_{i,\mathrm{gas}} \qquad (7)$$

The weighted mean Gibbs energy of conformational change for each compound is given by:

$$\Delta G_{\mathrm{conf}} = \sum_{\mathrm{i}} x_{i,\mathrm{sol}} G_{i,\mathrm{int}} - \sum_{\mathrm{i}} x_{i,\mathrm{gas}} G_{i,\mathrm{gas}} \qquad (8)$$

where i stands for each conformer of a given compound and x_i for its molar fraction calculated from the Boltzmann distribution based on the Gibbs energy.

3. Computational Method

The G_{gas} values for all possible conformers of each molecule were determined by DFT calculations using the B3LYP hybrid functional[9−11] and the Dunning's correlation consistent polarized valence double-ζ basis set (aug-cc-pVDZ).[12,13] These calculations involved full geometry optimization enabling the determination of the electronic energy followed by vibrational frequency calculations. The values of the electronic energy were then corrected with the zero-point vibrational energy, as well as the translational, rotational, and vibrational energies at 298.15 K, thus allowing the computation of the Gibbs energy at the same temperature. Details of these calculations have been given in a previous work.[14]

To obtain the Gibbs energies in aqueous solution, the conductor-like polarizable continuum model (CPCM)[5,15−17] was employed, treating the solute at the same level of theory as that used in the gas-phase calculations. According to this model, the solute molecule is placed into a cavity surrounded by the solvent considered as a continuum medium of a certain dielectric constant. The charge distribution of the solute polarizes the dielectric continuum, which creates an electrostatic field that in turn polarizes the solute.

All structures obtained by the DFT calculations performed in the isolated molecules were fully optimized in solution using the dielectric constant of water at 298.15 K ($\epsilon = 78.4$) to simulate the aqueous environment. The cavity was built according to the united atom topological model (UAHF),[18] in which the van der Waals surface is build by putting a sphere at each atom, except for hydrogen atoms which were enclosed in the sphere of the atom to which they were bonded. The number of surface elements (tesserae) for each sphere was 60, and an area of 0.4 Å^2 was set for each tessera. Tight SCF convergence criteria were used in all calculations. The calculations were performed using the Gaussian 03 program package.[19]

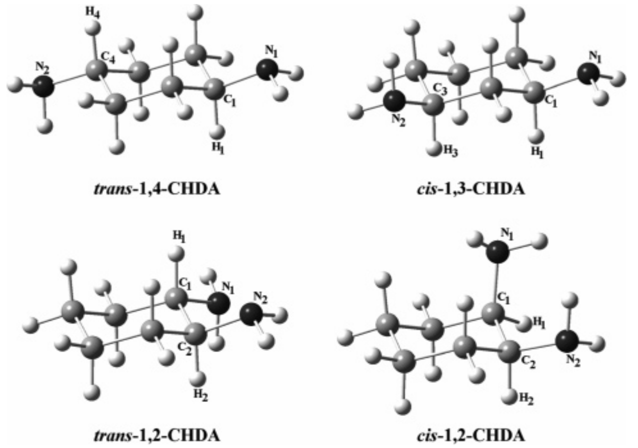
trans-1,4-CHDA *cis*-1,3-CHDA *trans*-1,2-CHDA *cis*-1,2-CHDA

Figure 1. CPCM/B3LYP/aug-cc-pVDZ optimized structures with atom numbering scheme for the most stable conformers of CHDA isomers in aqueous solution.

4. Results and Discussion

The conformers of CHA and CHDA are identified by the torsional angles formed by the nitrogen lone-pair (Lp), nitrogen, carbon and hydrogen atoms (θ). The structure and atom numbering scheme of the diamines are displayed in Figure 1. Torsional angles with $\theta = 180 \pm 30°$ are called anti (a), $\theta = 60 \pm 30°$ gauche+ (g$^+$) and $\theta = -60 \pm 30°$ gauche− (g$^-$). In the case of CHDA isomers, the nitrogen atom bonded to C_1 is designated as N_1 and the second nitrogen as N_2, independent of what carbon atom it is connected to. The conformers are numbered following the increase of G_{sol}.

The characterization of the conformers and the quantities required to calculate the solvation Gibbs energy at 298.15 K for the amines under investigation are presented in Table 1. To simplify the comparison of the Gibbs energies among conformers, these are expressed in relative terms. The absolute values for the lowest Gibbs energy conformer of every compound are given in Table 2.

Except for *cis*-1,2-CHDA, in which one of the amine groups is equatorial and the other is axial, for all the other diamines studied both groups have the same position relative to the cyclohexane ring. Thus, the structure of the latter, as well as that of CHA, can be considered as a dynamic equilibrium between di-equatorial and di-axial conformers, which can interconvert by ring flipping. The results displayed in Table 1 show that the contribution of the axial conformers, either in the gas or in aqueous solution, is small in the case of CHA and practically negligible in the diamines, which is in agreement with what is generally observed for mono- and disubstituted cyclohexanes.[20−22] However, despite their small or even negligible contribution in the gas and solution conformational populations, some axial conformers were included in Table 1 in order to understand the effect of this type of conformation on hydration.

TABLE 1: Degeneracy Factors (*g*), Dihedral Angles (θ/°), Relative Gibbs Energies in the Gas Phase ($G_{\mathrm{gas,rel}}$) and in Solution ($G_{\mathrm{sol,rel}}$), Relative Intrinsic Gibbs Energy in Solution ($G_{\mathrm{int,rel}}$), Molar Fractions (x/%), Calculated Solvation Free Energies (ΔG_{solv}), and Their Components for the Conformers of CHA and CHDA Isomers[a]

		gas phase				solution										
conformer[b]	*g*	θ_1[c]	θ_2[c]	$G_{\mathrm{gas,rel}}$[d]	x_{gas}	θ_1[c]	θ_2[c]	$G_{\mathrm{int,rel}}$[d]	$G_{\mathrm{sol,rel}}$[d]	x_{sol}	ΔG_{conf}	ΔG_{cav}	ΔG_{elec}	ΔG_{disp}	ΔG_{rep}	ΔG_{solv}
CHA																
I	2	−59.2		0.00	59.3	−59.7		0.00	0.00	64.4	0.35	64.60	−21.30	−83.89	19.70	−20.54
II	1	180.0		1.26	35.7	179.9		1.29	1.61	33.6	0.39	64.43	−20.63	−84.22	19.85	−20.18
III (ax)	2	−60.6		8.58	1.9	−60.2		8.54	9.79	1.2	0.31	64.10	−20.04	−82.68	18.98	−19.33
IV (ax)	1	180.0		7.32	3.1	180.0		7.63	11.11	0.7	0.67	63.76	−17.41	−83.97	20.20	−16.75
rrans-1,4-CHDA																
I	4	−179.7	59.6	0.00	47.8	180.0	59.6	0.00	0.00	45.7	0.77	68.37	−40.75	−101.75	30.55	−42.81
II	2	58.8	58.9	2.50	17.5	59.8	58.9	2.48	1.92	21.1	0.74	68.53	−41.67	−101.38	30.39	−43.39
III	2	−59.2	59.2	2.37	18.4	−59.6	59.2	2.36	1.94	20.9	0.75	68.53	−41.51	−101.42	30.41	−43.24
IV	1	180.0	180.0	2.67	16.3	179.9	180.0	2.69	3.26	12.3	0.79	68.20	−39.87	−102.09	30.76	−42.21
V (ax)	1	180.0	180.0	13.14	0.5^{e}	179.9	180.0	13.26	20.99	0.02^{e}	0.89	67.45	−33.10	−100.46	30.27	−34.95
VI (ax)	1	61.1	−61.3	20.37	0.03^{e}	60.5	−60.5	20.31	21.34	0.02^{e}	0.70	68.16	−40.71	−98.20	28.21	−41.84
cis-1,3-CHDA																
I	2	179.2	58.6	0.00	28.9	179.6	59.4	0.00	0.00	23.8	0.87	68.99	−42.43	−101.55	31.79	−42.33
II	2	60.1	−179.9	0.59	22.8	60.5	−179.7	0.54	0.32	21.0	0.83	68.95	−42.63	−101.75	32.00	−42.60
III	2	−59.4	−59.6	0.94	19.8	−59.6	−60.1	0.92	0.35	20.7	0.85	69.12	−43.30	−101.34	31.76	−42.91
IV	1	179.4	−179.3	2.06	12.6	179.6	−179.6	2.03	1.50	13.0	0.85	68.83	−42.59	−101.96	31.98	−42.89
V	1	−59.0	58.8	3.01	8.6	−59.6	59.2	2.98	1.51	13.0	0.84	69.16	−44.22	−101.21	31.60	−43.83
VI	1	59.7	−59.8	3.42	7.3	60.5	−60.4	3.43	2.53	8.6	0.88	69.12	−43.60	−101.55	31.94	−43.21
VII (ax)	2	177.1	54.5	10.37	1.5^{e}	178.9	50.7	10.50	18.86	0.05^{e}	1.01	67.28	−33.43	−99.50	30.84	−33.83
VIII (ax)	2	−62.5	−44.2	23.12	0.009^{e}	−64.6	−49.3	22.99	26.20	0.003^{e}	0.75	68.91	−40.42	−98.32	29.83	−39.24
trans-1,2-CHDA																
I	2	69.9	−172.9	0.00	46.7	65.0	−175.6	0.00	0.00	27.5	1.53	70.42	−39.87	−95.94	27.78	−36.08
II	2	67.6	−47.6	1.04	30.7	65.4	−52.7	0.60	0.25	24.9	1.10	70.21	−39.95	−96.32	28.09	−36.87
III	2	168.1	−66.2	3.81	10.0	171.4	−66.1	3.33	0.40	23.4	1.06	70.37	−42.26	−95.98	27.31	−39.50
IV	1	−61.3	−61.1	5.91	4.3	−62.9	−62.9	5.43	1.24	16.7	1.05	70.58	−43.93	−95.69	27.23	−40.76
V	1	163.0	163.1	4.28	8.3	168.8	168.8	4.04	3.19	7.6	1.30	70.12	−39.71	−96.19	27.31	−37.17
VI (ax)	1	−176.5	−176.4	15.72	0.2^{e}	−177.5	−177.5	15.33	16.93	0.1^{e}	1.14	69.04	−36.99	−96.65	28.83	−34.63
VII (ax)	1	59.1	59.1	21.06	0.02^{e}	59.1	59.1	19.53	19.20	0.1^{e}	0.50	69.58	−41.46	−94.27	26.40	−39.70
cis-1,2- CHDA																
I	1	62.9	−58.6	5.36	4.1	66.0	−58.1	4.64	0.00	20.7	1.06	70.00	−43.10	−94.81	26.91	−39.94
II	1	66.7	69.7	4.82	5.1	66.4	67.8	3.98	0.26	18.6	0.94	69.91	−42.05	−94.85	26.90	−39.15
III	1	−78.7	47.6	2.97	10.8	−69.1	53.1	3.21	1.48	11.4	2.01	69.75	−39.66	−94.98	26.80	−36.08
IV	1	−74.1	−74.1	3.05	10.5	−68.9	−68.1	2.43	1.58	10.9	1.16	69.79	−38.91	−95.19	27.10	−36.05
V	1	−171.6	−55.3	4.04	7.0	−171.9	−56.4	3.29	1.58	10.9	1.02	69.54	−39.62	−95.98	27.99	−37.05
VI	1	−166.9	75.3	2.02	15.8	−170.1	69.1	1.42	2.01	9.2	1.17	69.45	−37.15	−96.02	27.95	−34.60
VII	1	44.9	170.0	2.94	10.9	51.7	174.2	2.38	2.01	9.2	1.21	69.66	−38.20	−95.19	27.01	−35.51
VIII	1	169.3	167.2	0.00	35.8	172.7	174.8	0.00	2.03	9.1	1.77	69.20	−35.23	−96.65	28.36	−32.55

[a] All energy values are in kJ mol^{-1} and are referred to the temperature of 298.15 K. [b] The (ax) designation is used to identify the di-axial conformers. [c] $\theta_1 = \mathrm{Lp{-}N_1{-}C_1{-}H_1}$; $\theta_2 = \mathrm{Lp{-}N_2{-}C_2{-}H_2}$ for *trans*- and *cis*-1,2-CHDA, $\theta_2 = \mathrm{Lp{-}N_2{-}C_3{-}H_3}$ for *cis*-1,3-CHDA, and $\theta_2 = \mathrm{Lp{-}N_2{-}C_4{-}H_4}$ for *trans*-1,4-CHDA. [d] Values relative the most stable conformer in the gas phase, including a term accounting for the degeneracy degree ($-RT \ln g$). The absolute Gibbs energy values for the lowest energy conformers are given in Table 2. [e] Boltzmann populations relative to the lowest Gibbs energy conformer.

TABLE 2: Absolute Values (Hartrees) of G_{gas}, G_{int}, and G_{sol} for the Conformers of Each Compound Presenting the Lowest Gibbs Energy

compound	conformer	G_{gas}	G_{int}	G_{sol}
CHA	I	−291.1079955	−291.1078613	−291.1158183
trans-1,4-CHDA	I	−346.4545539	−346.4542622	−346.4708592
cis-1,3- CHDA	I	−346.4538035	−346.4534706	−346.4699246
trans-1,2-CHDA	I	−346.4545755	−346.4539910	−346.4683194
cis-1,2-CHDA	I	−	−	−346.4645927
	VII	−346.4493790	−346.4489767	−

The solvation Gibbs energy of each compound was determined by eq 2, with G_{sol} and G_{gas} taken from eqs 6 and 7, respectively. The values obtained for this property, as well as those obtained for ΔG_{conf}, given by eq 8, are presented in Table 3.

A discussion of the results obtained for the different compounds will first be presented, followed by the analysis of the data found for the conformers of each one of them. This methodology allows a general outlook on the hydration of the solutes and subsequently a detailed analysis of the results obtained for the individual conformers.

The variation of the solute molecular conformation accompanying the gas to solution transference gives a small contribution to the Gibbs energy of solvation. The values found for this property vary from ca. 0.1 kJ mol^{-1} in CHA to ca. 2.8 kJ mol^{-1} in *cis*-1,2-CHDA. Considering that the structure of the solute molecules is characterized by a rigid central nonpolar part to which the polar groups are attached, only changes in the orientation of these groups occur on solvation. Therefore, a small value would be expected for ΔG_{conf}. Although small, the differences between the isomers are meaningful. The values obtained for 1,3- and 1,4-CHDA are higher than that obtained

TABLE 3: Weighted Mean Values of the Gibbs Energy of Solvation (ΔG_{solv}) and Conformational Change Gibbs Energy (ΔG_{conf}) of CHA and CHDA Isomers

compound	ΔG_{solv} (kJ mol^{-1})	ΔG_{conf} (kJ mol^{-1})
CHA	−20.85	0.11
trans-1,4-CHDA	−42.73	0.80
cis-1,3- CHDA	−42.36	1.03
trans-1,2-CHDA	−36.05	2.37
cis-1,2-CHDA	−34.92	2.78

for CHA and lower than those reported for the 1,2-diamines. Hence, ΔG_{conf} is effectively dependent only on the polar groups. When the polar groups are close to each other, as in vicinal isomers, their mutual interference is unfavorable to hydration, leading to a higher conformational rearrangement on solvation when compared with the non-vicinal isomers. This structural interference, already shown to be present between the amino groups of the isolated 1,2-CHDA,[14] is certainly more pronounced when these groups are hydrated.

Comparison between the values of ΔG_{solv} obtained for monofunctional and difunctional amines indicates the minimal influence of the nonpolar part. This is confirmed from the values determined by the authors for cyclohexane: $\Delta G_{\mathrm{cav}} = 60.5$ kJ mol^{-1}, $\Delta G_{\mathrm{disp}} = -67.5$ kJ mol^{-1}, $\Delta G_{\mathrm{rep}} = 9.8$ kJ mol^{-1}, and $\Delta G_{\mathrm{solv}} = 2.8$ kJ mol^{-1}. The large negative value obtained for ΔG_{disp}, due to van der Waals attractive interactions between cyclohexane and water, is slightly outweighed by the positive terms resulting from the cavity formation and the solute−solvent repulsive forces. This feature, found in cyclohexane, is also manifested in the amines. The experimental value of ΔG_{solv} of cyclohexane, determined from the distribution coefficient of the compound between gas and water phases, is 5.14 kJ mol^{-1},[23] a value that corroborates the conclusion given above for the hydration Gibbs energy of nonpolar groups.

From the ΔG_{solv} values presented in Table 3, the solvation of CHDA isomers is ordered as follows:

trans-1,4-CHDA ≈
cis-1,3-CHDA > *trans*-1,2-CHDA > *cis*-1,2-CHDA

ΔG_{solv} per amine group in 1,3- and 1,4-CHDA is slightly more negative than that calculated for CHA, which means that, in these difunctional compounds, the hydration layers are not disturbed by mutual influence of the polar groups. In a previous work, it was shown that there is no interaction between the amino groups in the isolated 1,3- and 1,4-CHDA.[24] The results obtained in this work show that the same happens in solution. In contrast, in *cis*- and *trans*-1,2-CHDA, the proximity of both groups gives rise to an interaction between their hydrogen atoms. It is reasonable to accept that in solution the interaction between the polar groups provides a significant contribution for a decrease in the hydration of these diamines. The decrease of solvation of *cis*-1,2-CHDA relative to *trans*-1,2-CHDA (ΔG_{solv} difference ca. 1 kJ mol^{-1}) can be understood by a more pronounced group interference in the first isomer and/or because, in this isomer, one of the amine groups is axially oriented.

Considering the results obtained for CHA, *trans*-1,4-CHDA and *cis*-1,3-CHDA, the value to be tabled for the hydration Gibbs energy of the amine group is $\Delta G_{\mathrm{solv}} = -21.1 \pm 0.2$ kJ mol^{-1}. This figure is of the order of magnitude of those found experimentally for ammonia and small mono- and diamines.[25−28]

Amine groups are able to interact with water by hydrogen bonding, with both groups acting as proton donors or acceptors. The dipole moment of NH_2, determined by the authors from the values reported for the isolated equatorial CHA, is 1.204 D for the anti and 1.295 D for the gauche conformation. In aqueous solution, this molecular property increases to 1.953 and 1.865 D, respectively. Water also has a high dipole moment, 1.834 D.[29] Hence, hydrogen bonding between the amine group and water molecules plays an important role in the solvation of the solutes under consideration, as shown by the high negative values of ΔG_{elec}.

As a consequence of the weight of the nonpolar part in these molecules, a significant contribution of the van der Waals attractive interactions with water would be expected. In fact, ΔG_{disp} is the most significant term involved in eq 5. However, as stressed before, the contribution of this thermodynamic quantity is almost canceled out by the Gibbs energy required for the cavity formation and by that due to solute−solvent repulsion. Thus, the nonelectrostatic contribution is very small and ΔG_{elec} is, by far, the most influent quantity in ΔG_{solv}.

At a first glance, one can see from Table 1 that the factors affecting the solute−solvent interactions of the different conformers are the NH_2 orientation (gauche or anti), the position of this group relatively to the ring (axial or equatorial), and the distance between the groups. Their importance in understanding hydration will be the matter of consideration in the following discussion.

Considering the orientation of the polar groups it is clear that the gauche+ or gauche− conformers have a more favorable interaction with water than those with an anti conformation. In the equatorial CHA, the value of ΔG_{solv} for the gauche− conformer is ca. 0.4 kJ mol^{-1} more negative than that of the *anti* conformer. Likewise, in *trans*-1,4-CHDA, the hydration of the equatorial conformers is ordered as follows:

$$(g^+,g^+) \approx (g^-,g^+) > (a,g^+) > (a,a)$$

The hydration decreases from gauche to anti conformations, while practically no significant difference exists between gauche+ and gauche−. Although in *cis*-1,3-CHDA the polar groups are closer to each another, for the three most hydrated conformers, the two NH_2 groups also assume a gauche orientation.

The conformational preference of NH_2 lies in the hydrogen-bonding network of this group with water. In a study dedicated to the hydration of amines, Marten et al.,[30] using quantum chemical and molecular mechanics methods, proved that the hydrogen bond involving the lone electron pair of the nitrogen is much stronger than those with the amine group acting as proton donor. On the basis of this conclusion, it is reasonable that the differences in hydration related to the amine conformation depend on the Lp orientation. In the anti conformers, as the Lp points inward the ring, hydration becomes more difficult due to the close proximity to the crowded CH axial group space. In contrast, when the amine groups adopt a gauche+ or gauche− orientation, Lp points outward, and there is no constraining effect on the hydration layer.

Comparing the values of ΔG_{solv} between axial and equatorial configurations of conformers with identical NH_2 orientation, one can see that the former disfavors the interaction with water relative to the equatorial one (see, for example, the following pairs of conformers: V/IV of *trans*-1,4-CHDA, VII/I and VIII/III of *cis*-1,3-CHDA). Also, in the di-axial conformers the difference between the anti and gauche orientations is higher than in the equatorial ones (compare, for example, ΔG_{solv} difference between conformers VI and V with that between conformers IV and III of *trans*-1,4-CHDA).

We are not aware of any study on the equatorial/axial solute conformation involving amines. However, this effect has been extensively studied in hydroxylated derivatives of cyclohexane, particularly carbohydrates. In view of the structure similarity, the interpretation given for the hydroxylated compounds is relevant to the understanding of the behavior in cyclohexylamines.

Since 1958, it has been accepted that in hydroxylated compounds the preference for the equatorial configuration results from its better adaptability to an ice-like structure of water.[31−34] With the development of new models for water structure,[35,36] citations of this theory have been declining. Nevertheless, Chaplin claims that his proposal of a fluctuating network of water molecules with localized icosahedral symmetry explains the carbohydrate hydration.[37] However, at the same time, different interpretations based on the structural features of the solute and data proving that higher hydration of equatorial conformers is not a rule have been published.[38,39]

The results obtained in this work show a decrease of the hydration of the axial amine group relatively to the equatorial one. However, in some cases, the differences between axial conformers of an isomer are higher than those between axial and equatorial conformers with the same NH_2 orientation. For example, ΔG_{solv} of conformer VI of *trans*-1,4-CHDA (g^+,g^-) is 1.4 kJ mol^{-1} higher than that of conformer III (g^-,g^+), while the difference of this function between conformers V and VI is 7.3 kJ mol^{-1}. The proximity between the axial NH_2 group and the C−H groups makes hydration more difficult, in particular when the polar group is anti, because the Lp of the nitrogen points toward the middle of the H_3...H_5 distance. When the orientation is gauche, only one of the hydrogen atoms of the amine group points to the inside of the ring and no space restrictions are imposed to the interaction between Lp and water. Hence, one can conclude that the effect of the equatorial/axial position of the NH_2 group on hydration is related with the crowding of the C−H groups in this position making more difficult the interaction of the Lp and water, rather than with the proper structure of water.

The hydration ordering based on the results obtained for the conformers of the non-vicinal CHDA isomers cannot be taken as a rule. In fact, the relative NH_2 orientations in the vicinal isomers can give rise to significant differences in hydration. For example, in the four most stable conformers of *cis*-1,2-CHDA the two NH_2 groups assume a g^+ or g^- orientation. The ΔG_{solv} difference between the first two conformers, (g^+,g^-) and (g^+,g^+), is small. Also, values obtained for conformers (g^-,g^+) and (g^-,g^-) are close. However, the difference between both pairs is higher than 3 kJ mol^{-1}. In some orientations, the Lp of one group points toward the hydrogen of the other and the hydration is disfavored. This is the case of (g^-,g^+) and (g^-,g^-). In the other orientations, (g^+,g^-) and (g^+,g^+), no interference occurs. Other examples leaving out the ordering referred above can be seen in *trans*-1,2-CHDA. Conformers II (g^+,g^-) and IV (g^-,g^-) show a difference in ΔG_{solv} of ca. 4 kJ mol^{-1}, with IV being the favorable structure. The solvation Gibbs energy of conformer III (a,g^-) is ca. 3.4 kJ mol^{-1} more negative than conformer I (g^+,a). The explanation for the relative effect of the NH_2 orientation in this isomer is the same as that given for *cis*-1,2-CHDA.

The proximity effect of the amine groups on hydration is also manifested in the conformational distribution in solution when compared with that existing in the gas phase. In CHA, *cis*-1,3-CHDA and *trans*-1,4-CHDA, since the difference of ΔG_{solv} between the conformers is small, the conformational population in solution remains identical to that in the gas phase. In contrast, the transference of 1,2-diamines from the gas phase to solution is accompanied by significant conformational distribution changes. The most pronounced effects occur in *cis*-1,2-CHDA. For this isomer, the two less abundant conformers in the gas phase (I and II), with $G_{gas,rel}$ values of 5.36 and 4.82 kJ mol^{-1}, respectively, are, by far, those exhibiting the lowest ΔG_{solv} values. The difference of ΔG_{solv} between these conformers and the three most stable ones in the gas phase (VIII, VI and VII) lies between 5 and 7 kJ mol^{-1}, which is big enough to invert the conformational stability in solution from that existing in the gas phase. Therefore, conformers I and II become the two most populated conformers in solution, while conformers VI, VII and VIII the less abundant ones.

5. Concluding Remarks

Values of the solvation Gibbs energy of the conformers of cyclohexylamine and cyclohexyldiamines are given for the first time in the present work. The determination of the solvation Gibbs energy of a compound from that of the respective conformers allows the establishment of relationships between solvation and structural details, which are difficult to achieve by other routes.

The solute−solvent interactions which account for the Gibbs energy of solvation are mainly due to the interaction of the amine groups with water. In cyclohexylamine and nonvicinal cyclohexyldiamines, the estimated value of ΔG_{solv} per group is ca. 21 kJ mol^{-1}. When the amine groups are bonded to vicinal carbon atoms, their mutual interference in hydration increases this value to ca. 18 kJ mol^{-1}.

The results obtained for the solvation Gibbs energy of the isomers and conformers of cyclohexylamines have shown the ability of the CPCM solvation model, in conjunction with the DFT/B3LYP method, to investigate this thermodynamic function. Considering the structural similarity between conformers, it was possible to discriminate between small differences in hydration resulting from the different NH_2 orientations.

The following predominant structural patterns on hydration were underlined: the spatial orientation of the NH_2 group—gauche is preferred to anti—the equatorial configuration of the NH_2 groups is preferred to axial, polar groups connected to remote carbon atoms interact more strongly with water than the vicinal ones. Further, in vicinal diamines, the hydration also depends on the relative orientation of both groups.

Unlike the 1,3- and 1,4-CHDA, where the conformational distribution in the aqueous solution closely resembles that in the gas phase, in *cis*-1,2-CHDA, an almost complete inversion of the conformational stability order occurs, with the most stable conformer in solution being the least stable in the gas phase and vice versa.

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