Journal of the Argentine Chemical Society

A DFT STUDY OF HYDROGEN BOND FORMATION INTO NUCLEOPHILIC DIAMINES IN APROTIC SOLVENT MEDIA

Federico Bergero[1], Cecilia E. S. Alvaro[2,♥], Norma S. Nudelman[3,4] and Susana Ramos de Debiaggi[1,4]

[1]*Depto. de Física, Facultad de Ingeniería, Universidad Nacional del Comahue, Buenos Aires 1400, (8300) Neuquén, Argentina.*

[2]*Depto. de Química, Facultad de Ingeniería. Universidad Nacional del Comahue, Buenos Aires 1400, (8300) Neuquén, Argentina*

[3]*Depto. de Química Orgánica. Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Ciudad Universitaria, (1428) Buenos Aires, Argentina*

[4]*National Research Council of Argentina (CONICET).*

Abstract

A detailed theoretical study on 3-dimethylamino-l-propylamine (DMPA), 1-(2-aminoethyl)-piperidine (2-AEPip) and 3-(aminopropyl)-morpholine (3-APMo) is presented. These are special

♥ Corresponding author: E-mail*: silvana_alvaro@hotmail.com* Fax: 0299-4490300/385

nucleophiles of appropriate flexible structure, regarding their inter- and intramolecular hydrogen bond (H-bond) self-aggregation states, that are of interest in connection with our last studies of Aromatic Nucleophilic Substitution (ANS) carried out in aprotic solvents.
According to kinetic results, ANS reactions of 1-halo-2,4-dinitrobenzenes with DMPA and 2-AEPip in toluene are third-order in amine (overall fourth order kinetics), results that can be interpreted in terms of the "*dimer nucleophile mechanism"*. By contrast, the reactions with 3-APMo shows second-order in amine, consistent with the classical ANS mechanism, suggesting that this diamine reacts in the monomeric state due to an internal H-bond formation ("intramolecular dimer").

To provide valuable insight into the predominant type of H-bond formed we performed *ab initio* Density Funcional Theory calculations on the above mentioned amines determining the optimal geometry and its corresponding energy in vacuum for monomers and dimers at the B3LYP/6-31++G(d) level. We implemented a methodology to simultaneously evaluate Counterpoise corrections and solvent effects within the polarized continuum model (PCM). In all cases we found that solvation energies are favorable and H-bonded dimers are more stable than their monomers. Consistent with kinetic results, for 3-APMo the dimerization energy is much lower than for 2-AEPip and DMPA. These theoretical findings are significant and are in line with available experimental results that shows the nucleophile structure is crucial to determine the predominant type of H-bonds in ANS reactions of diamines in aprotic solvents.

Key words: diamines, DFT calculations, hydrogen bond, aprotic solvents, Counterpoise correction method, polarizable continuum model

Resumen

Realizamos un estudio teórico detallado de las moléculas 3-dimetilamino-l-propilamina (DMPA), 1-(2-aminoetil)-piperidina (2-AEPip) y 3-(aminopropil)-morfolina (3-APMo). En estudios cinéticos previos, utilizamos estas diaminas como nucleófilos en reacciones de Sustitución Nucleofílica Aromática (S_NAr) realizadas en solventes apróticos, debido a que presentan apropiadas estructuras flexibles que pueden formar uniones hidrógeno (unión-H) inter- e intramoleculares.

De acuerdo a dichos resultados, las reacciones de 1-halo-2,4-dinitrobencenos con DMPA y 2-AEPip en tolueno presentan cinéticas de tercer orden en amina (cuarto orden global), resultados que pueden ser interpretados en términos del "mecanismo del dímero nucleófilo". Por el contrario, las reacciones con 3-APMo muestran segundo orden en amina, de acuerdo al mecanismo clásico de descomposición base catalizada del intermediario zwitteriónico, sugiriendo que 3-APMo reacciona en estado monomérico debido a la formación de unión-H intramolecular ("dímero intramolecular").

Desarrollamos cálculos *ab initio* basados en la Teoría de la Funcional Densidad en las aminas mencionadas, analizando el tipo predominante de unión-H formada. Considerando cálculos al nivel B3LYP/6-31++G(d) determinamos sus geometrías óptimas y energías en vacío para los monómeros y dímeros. Implementamos una metodología para evaluar simultáneamente correcciones por error de superposición de bases y efectos del solvente mediante el modelo de polarización del continuo (PCM). Consistente con los resultados cinéticos, la energía de dimerización de 3-APMo es mucho menor que para 2-AEPip y DMPA. Los resultados teóricos presentados concuerdan con los obtenidos experimentalmente, sugiriendo el efecto crucial de la estructura del nucleófilo en determinar el tipo de unión-H predominante en las reacciones de S_NAr realizadas en solventes apróticos.

Palabras clave: diaminas, cálculos DFT, unión hidrógeno, solventes apróticos, método Counterpoise, modelo polarizable continuo

INTRODUCTION

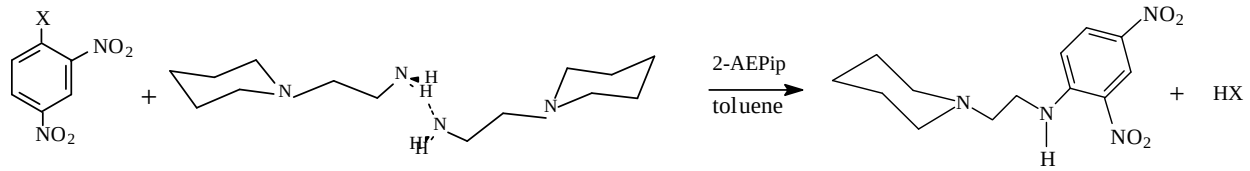
Though noncovalent interactions are the key to many phenomena in chemistry and biology, the understanding of such interactions is still hampered by the fact that are usually indirectly inferred. A detailed and reliable assessment of weak interactions in molecular complexes is therefore needed, so accurate computational approaches of them and solvation effects between molecular species are valuable to study complex organic mechanistic pathways and biological systems [1].

One of the most important types of noncovalent interactions, having a dominant role in the properties and reactivity of molecules, is hydrogen bonding (H-bonding). In the last years many theoretical and experimental investigations were performed to determine the existence of H-bond interactions in molecular structures of organic and biological compounds, such as solute-solute and solute-solvent H-bond interactions [2-13]. In this way, new types of H-bond interactions were found by theoretical calculations [5], and related with experimental studies. Recently, Řezáč and Hobza [12b] introduced a new generation of H-bonding and dispersion forces corrections to semiempirical quantum mechanical methods (SQM) that improve its accuracy and for the first time can be used for geometry optimization and molecular-dynamics simulations without any limitations. Combining contemporary *ab initio* theoretical and experimental research methods seems nowadays mandatory for precise conclusions on the structure and reactivity of molecules [14]. *Ab initio* quantum mechanical methods, in particular density functional theory (DFT) [15], arguably offer the most accurate methods for determining the stability and properties of structures. Therefore, the use and development of computational methods to include corrections for non-covalent interactions is now a current field of study [16].

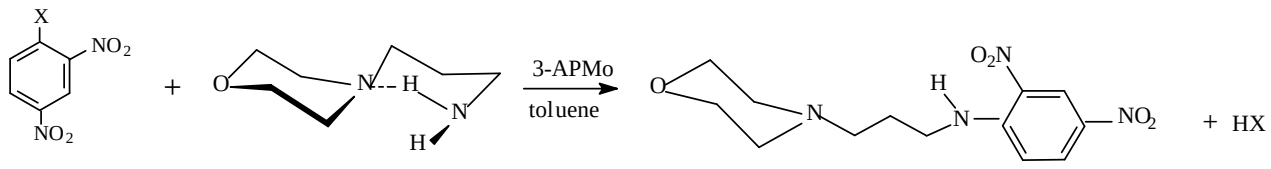
Self-association of amines to form mainly dimers by H-bonding interactions is a long known phenomenon [17]. It has been shown that dimers are responsible for the so-called "dimer nucleophile" mechanism when amines are used as nucleophilic reagents in reactions carried out in aprotic solvents [9, 18, 19]. In Nudelman's mechanism [9], the dimer of the amine acts as a nucleophile forming an intermediate complex, and a third molecule of amine assists the decomposition step. The reaction with the monomer nucleophile is also possible, but the reaction with the dimer is faster because of its higher donicity [9].

Intermolecular hydrogen bonding increases the nucleophilicity of the dimer compared with the monomer, as it was confirmed by semiempirical and *ab initio* calculations [20]. On the other hand, when two amino groups in the molecule are in a convenient geometry, intramolecular hydrogen bonding is easily established, and those compounds exhibit unusually high basicity.

We have published unusual findings in ANS carried out in aprotic solvents using mono-[18] and polyfunctionalized [13,19] amines that would be able to form intra- or intermolecular H-bond (Scheme 1). These kinetic results were lately confirmed by variable-concentration nucleophiles ^{1}H-NMR studies [21].



X = F, Cl — 2-AEPip intermolecular dimer — N-(2,4-dinitrophenyl)-2-aminoethylpiperidine



X = F, Cl — 3-APMo intramolecular dimer — N-(2,4-dinitrophenyl)-3-(aminopropyl)-morpholine

Scheme 1

Recently we reported theoretical [10] and experimental results [13, 19] of mixed dimers formed by the aggregation of the nucleophile and a dipolar-aprotic molecule of solvent; additional evidence for the dimer mechanism was provided through the treatment of the kinetic results and calculations of the different *k's*, considering a reaction pathway including the monomer and the dimer nucleophile for reactions where the first step is the rate determining step (r.d.s.) [22].

Gas-phase experiments demonstrate that, in vacuum, the hydrogen bonding interaction within dimers of amines are stable [8]. The situation is the same in organic solvents; H-bonded structures of diamines have been detected in chloroform and DMSO solutions by nuclear magnetic resonance experiments [21].

In order to analyze the nucleophile structure effects due to its self-aggregation states and correlate with kinetic results, the present work reports results of DFT calculations performed on diamines of flexible structure usually employed in mechanistic studies, analyzing their stability and H-bond formation. The amines studied in this work are 3-dimethylamino-l-propylamine (DMPA), 1-(2-aminoethyl)-piperidine (2-AEPip) and 3-(aminopropyl)-morpholine (3-APMo).

While the computational literature on non-covalents interactions in the gas phase is abundant, studies of these interaction types in organic solvents are still few, and further work is required for a detailed understanding of their stability in solution. Consequently, the study of solvent role in the formation and stabilization of H-bonds in vacuum and toluene was carried out with the continuum solvent model, including the Counterpoise [23] method to account for basis set superposition errors (BSSE).

COMPUTATIONAL DETAILS

Calculations were performed using Gaussian 09 [24]. The semiempirical Austin Method 1 (AM1) [25] was used with a Monte Carlo algorithm for an automatic search of equilibrium conformers of monomers and dimers. A selection of these conformers were then used for further *ab initio* optimizations using the DFT [15], the diffuse atomic orbital basis set 6-31++G(d) and the hybrid exchange-correlation functional B3LYP [26]. Convergence criteria are 1.5×10^{-5} a.u. for forces and 10^{-6} a.u. for the total energy.

All optimized geometries, in vacuum and in solution, were confirmed to be potential energy minima by computing vibrational frequencies. For dimers in vacuum, the basis set superposition error (BSSE) was corrected with the Counterpoise method [23] as implemented in the software.

This level of calculation has shown to provide reliable structural and energetic information on both intra- and intermolecular hydrogen bonds in good agreement with higher level *ab initio* calculations [27-32].

In order to take into account solvent effects, we further optimized the geometries with the integral equation formalism variant (IEFPCM) [33] of the polarized continuum model (PCM). The final energy of these geometries was then calculated using the self-consistent solvation model based on solute electron density (SMD) [34], which includes non-electrostatic energy terms, and is the recommended model for computing solvation energies [24]. The calculations were done in this way because the software does not perform geometry optimizations with SMD.

To evaluate the BSSE correction, we applied the Counterpoise procedure while considering the SMD model for computing the energies in the presence of solvent. This procedure is not automatically available in usual software packages; in the following section we describe in detail how it was implemented "manually".

The Counterpoise correction method in solution

This method is based on the one described by Wang and Newton [35]. Instead of using the PCM model as done in the cited work, we used the SMD model, and a different approach to generate the software input.

We define the dimer's "Counterpoise-corrected energy" (E_{corr}) as the energy (E) calculated as default by the software with the SMD model, plus the basis set superposition error:

$$E_{corr} = E + BSSE$$

The BSSE is defined as follows:

$$BSSE = MCBS1 + MCBS2 – DCBS1 – DCBS2$$

DCBSn ("dimer-centered basis set") is the energy calculated for fragment "n", with the same geometry it has within the dimer, but including all the basis functions of the whole dimer, and its whole solute cavity (Figure 1b). This is accomplished by a standard single-point SMD calculation in which the opposite fragment (*i.e,* fragment 2 in DCBS1 and vice versa) is replaced by "ghost atoms" in all the same positions. The software treats these as basis functions centered in those positions, but with no corresponding electrons or nuclear charges, and also provides the corresponding spheres that add to the solute cavity.

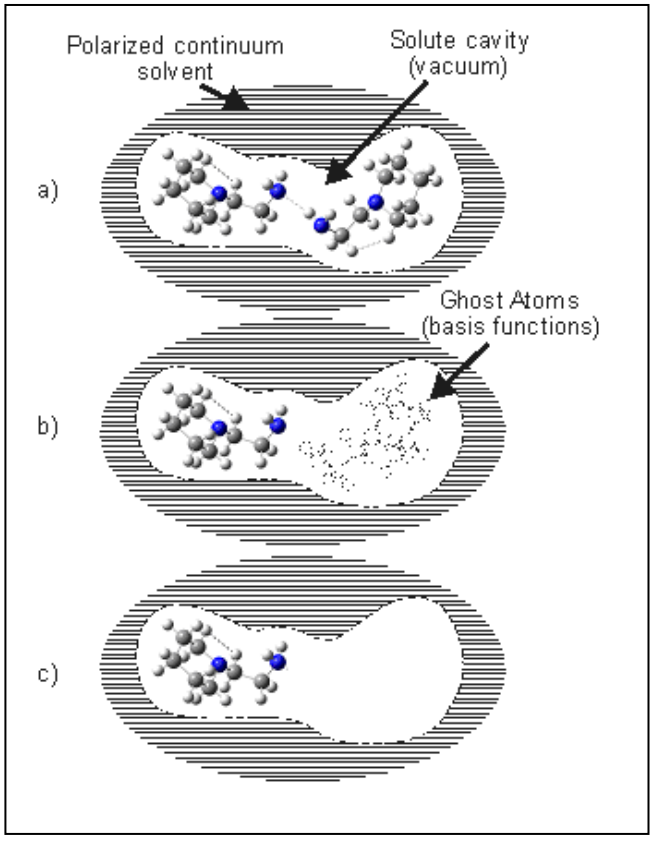


Figure 1. The Counterpoise method with PCM. a) Dimer calculation. b) DCBS calculation. c) MCBS calculation.

MCBSn ("monomer-centered basis set") is the energy calculated for fragment "n", in the corresponding dimer geometry, with only its own basis functions, but again considering the whole cavity corresponding to the dimer (Figure 1c). This is accomplished by a single-point SMD calculation in which the opposite fragment is replaced by "ghost atoms" and also those atoms are selected to have a user-defined basis set with zero basis functions, thus merely adding spheres to the solute cavity.

It should be noted that the present procedure is the same as the standard Counterpoise procedure included in the software package, but adding the SMD model with the dimer's solute cavity in all (E, DCBS and MCBS) calculations.

We define dimer formation energy as the Counterpoise-corrected dimer energy minus two times the monomer energy, thus including the geometry variation effect.

Hydrogen bond search and characterization

The presence of intra- and intermolecular hydrogen bonds, including non-conventional ones, was studied using the Atoms in Molecules theory (AIM) [36] with the AIM 2000 software [37]. According to this theory, a bond exists when there is a bond critical point (BCP) (a saddle point of the electron density ρ, being a minimum in the bond direction and a maximum in the other two perpendicular directions), and there is a bond path (along which ρ is a maximum in two directions) between two atoms. The density and its Laplacian $\nabla^2\rho$ at the BCP of hydrogen bonds have been found to be roughly proportional to the bond's stabilization energy [38]. The positive sign of the Laplacian found in all H-bonds also shows their closed-shell (non-covalent) nature [36]. The ellipticity ξ at the BCP shows the electron density's deviation from circular symmetry: $\xi = 0$ indicates a perfectly symmetric bond, *i.e.* a σ (or a double π) bond type, and $\xi = 1$ indicates a π bond. Higher values of ξ are indicative of a strained bond in a ring structure, which is about to be broken [36].

RESULTS AND DISCUSSION

Structure, H-bonding and energy of monomers

The DMPA, 2-AEPip and 3-APMo molecules were first calculated in vacuum and in toluene. Figures 2a-2c shows the optimized structures for the 2-AEPip, 3-APMo and DMPA molecules respectively. Dotted lines show the hydrogen bonds found. Geometries in vacuum and in toluene do not differ significantly, showing the same type of hydrogen bonds in both cases.

Table 1 shows, both in vacuum and in toluene, the dipolar moment (in Debye) of the molecules; for the intramolecular hydrogen bonds, the hydrogen-acceptor (or H-H) distance d and, if applies, donor-hydrogen-acceptor angle α and the bond's AIM characteristics: electron density, its Laplacian and the ellipticity at the BCP. The table also shows the solvation energy of the molecules (ΔE_{solv}), which is the SMD energy with non-electrostatic terms, calculated with the IEFPCM geometry, minus the energy in vacuum, in its own geometry, thus including geometric relaxation effects.

Figure 2 illustrates that 2-AEPip monomer has an intramolecular non-conventional hydrogen-hydrogen bond [39]. Its ellipticity is very high, especially in toluene, indicating that the bond is very strained. This may be due to the fact that the structure is not fully relaxed at the SMD level.

Both DMPA and 3-APMo have an intramolecular H-bond with the primary nitrogen acting as proton donor. No intramolecular H-bond between aliphatic N-H and oxygen alicyclic atom was found for any of the 3-APMo conformers analyzed. Open conformers with no intra-molecular H-bonding are found to be less stable.

With the exception of 3-APMo, in the other two molecules studied we find that almost all criteria (distance, angle, density, Laplacian) indicate that the bond is slightly stronger in toluene. For 3-APMo the Laplacian at the BCP slighlty decreases in toluene (by -0.5%)

In all cases, solvation stabilizes the molecules and the dipolar moment is increased with respect to vacumm values by about +0.3 to +0.4 Debye.

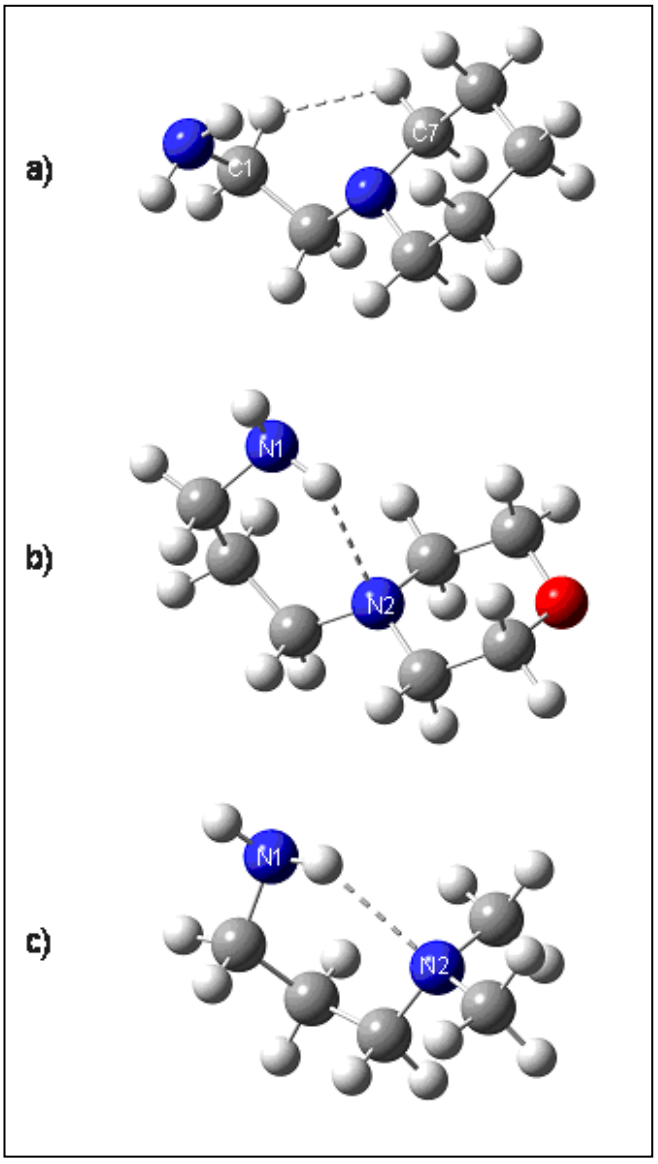


Figure 2. Monomer structure and H bonding. a) 2-AEPip. b) 3-APMo. c) DMPA.

Table 1: Monomer solvation energy, dipolar moment and H-bond characteristics for 2-AEPip, 3-APMo and DMPA. See definitions in text.

Vacuum							
		μ (D)	**d (Å)**	**α (º)**	**ρ (au)**	**$\nabla^2\rho$ (au)**	**ξ**
2-AEPip		2.073	2.179	-	0.009201	0.038703	4.574
3-APMo		2.024	2.339	124.96	0.015777	0.048580	0.067
DMPA		1.342	2.332	125.55	0.015866	0.049051	0.061
Toluene							
	ΔE_{solv} (kcal/mol)	**μ (D)**	**d (Å)**	**α (º)**	**ρ (au)**	**$\nabla^2\rho$ (au)**	**ξ**
2-AEPip	-6.384	2.372	2.176	-	0.009208	0.039141	5.881
3-APMo	-6.755	2.374	2.335	126.960	0.015953	0.048312	0.063
DMPA	-4.551	1.727	2.321	127.793	0.016289	0.049263	0.057

Structure, H-bonding and energy of dimers

Table 2 shows the dimer formation energies (ΔE_{dim}) for the 2-AEPip, 3-APMo and DMPA molecules, calculated in vacuum. For the latest, we report two conformers, named 1 and 2. The table also shows a list of the intra and inter-molecular hydrogen bonds found. The columns "frag. 1" and "frag. 2" show to which fragment do the H-bonded atoms belong. The H-acceptor (or H-H) distance, donor-H-acceptor angle (when applies), electron density, Laplacian and ellipticity of the hydrogen bonds at the BCP are also shown.

In a similar format, for the same dimers, Table 3 shows the same parameters calculated in toluene. In this case ΔE_{dim} is referred to twice the energy of the monomer in solution. The table also shows the dimer's solvation energy (as defined previously, including SMD energy and geometry variation). Solvation energies are negative in all cases. The corresponding structures for the dimers in solution are shown in Figures 3a-3d.

The structure of the molecules does not vary significantly with solvation and neither do the "conventional" (N-H…N), stronger hydrogen bonds. In 3-APMo, however, there are "non conventional", weaker hydrogen bonds that disappear by solvation; only the structure and H bonding in solution are shown.

As shown in Figure 3, the 2-AEPip dimer maintains the same intramolecular weak H-H onds and a stronger intermolecular H-bond is formed between the primary nitrogens of both monomers. In 3-APMo, the intramolecular H-bond of one monomer is broken to form the dimer; an intermolecular H-bond is formed between primary nitrogens and also a non-conventional intermolecular H-H bond of alicyclic carbons. In DMPA dimer 1, for one of the monomers the intramolecular H-bond is broken while for the other one it remains; and an intermolecular H-bond between the primary nitrogens is formed.

Table 2: Formation energy, H-bonds and H bond characteristics of dimers in vacuum for 2-AEPip, 3-APMo and DMPA. For DMPA two different conformers are considered. See definitions in text.

	ΔE_{dim} (kcal/mol)	Frag 1	Frag 2	D (Å)	α (º)	ρ (au)	$\nabla^2\rho$ (au)	ξ
2-AEPip	-2.940	N1-H…	...N1	2.250	156.438	0.01710	0.05055	0.012
		C1-H…H-C3		2.181	-	0.00915	0.03811	3.515
			C1-H…H-C7	2.145	-	0.00978	0.04157	3.049
3-APMo	-0.296	N1-H…	…N1	2.240	168.397	0.01824	0.05101	0.036
		C7-H…	…H-C5	3.817	-	0.00031	0.00096	0.203
		C2-H…	…H-C5	3.698	-	0.00040	0.00125	0.360
		C1-H…	…H-C5	3.916	-	0.00031	0.00113	1.215
			N1-H…N2	2.319	128.062	0.01644	0.04947	0.061
DMPA 1	-0.916	N1-H…	…N1	2.233	164.226	0.01839	0.05193	0.033
			N1-H…N2	2.337	132.348	0.01611	0.04729	0.102
DMPA 2	-0.362	N1-H…	…N1	2.293	141.523	0.01481	0.04747	0.050
		N2…	…H-N1	2.328	154.666	0.01555	0.04410	0.002
		C4-H…	…H-C2	3.081	-	0.00137	0.00449	11.153

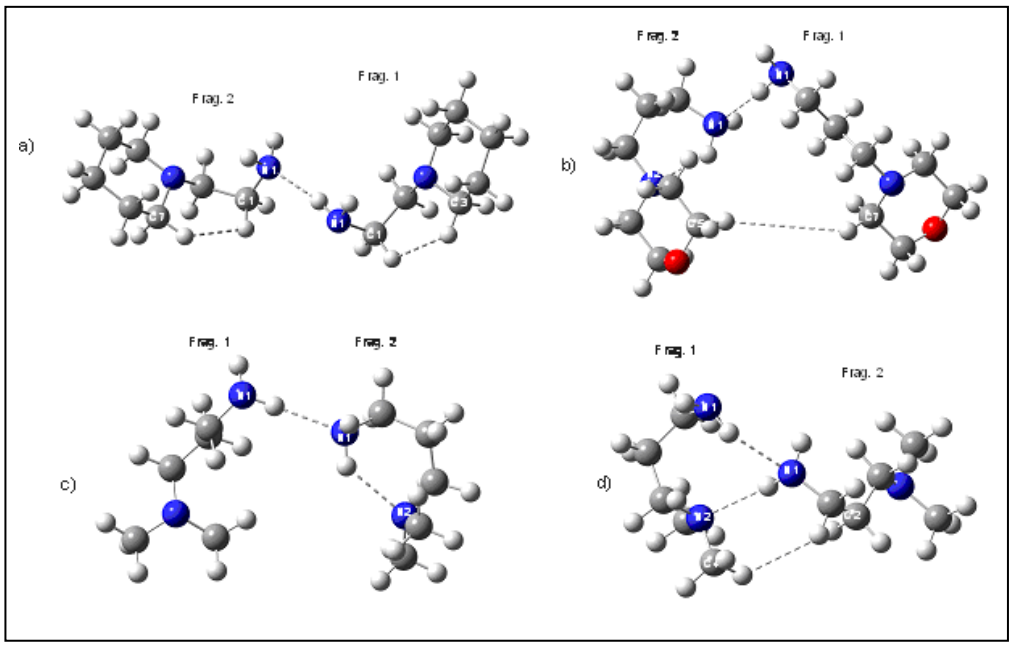


Figure 3. Dimer structure and H bonding in solution. a) 2-AEPip. b) 3-APMo. c) DMPA 1. d) DMPA 2.

Table 3. Solvation energy, formation energy, H-bonds and H-bond characteristics of dimers in toluene for 2-AEPip, 3-APMo and DMPA. See definitions in text.

	ΔE_{solv} (kcal/mol)	ΔE_{dim} (kcal/mol)	Frag 1	Frag 2	D (Å)	α (º)	ρ (au)	$\nabla^2\rho$ (au)	ξ
2-AEPip	-11.851	-2.024	N1-H…	...N1	2.237	170.394	0.01850	0.05141	0.010
			C1-H…H-C3		2.182	-	0.00908	0.03841	5.628
				C1-H…H-C7	2.174	-	0.00924	0.04006	42.646
3-APMo	-13.378	-0.163	N1-H…	...N1	2.230	171.577	0.01886	0.05153	0.031
				N1-H…N2	2.321	128.590	0.01637	0.04900	0.061
			C7-H…	…H-C5	3.996	-	0.00022	0.00071	0.233
DMPA 1	-8.875	-0.690	N1-H…	…N1	2.227	167.863	0.01890	0.05197	0.025
				N1-H…N2	2.321	132.813	0.01662	0.04841	0.095
DMPA 2	-9.193	-0.454	N1-H…	…N1	2.326	143.358	0.01386	0.04418	0.036
			N2…	…H-N1	2.318	157.564	0.01596	0.04454	0.002
			C4-H…	…H-C2	2.984	-	0.00159	0.00507	0.693

In DMPA's dimer 2 both intramolecular H-bonds are broken and two intermolecular H-bonds are formed: one between the primary nitrogens, in the other one the proton acceptor of the first H bond is also the proton donor to the other fragment's tertiary nitrogen. There is also an intermolecular "hydrogen-hydrogen" bond between the methyl group of the terciary nitrogen of frag. 1 with the methylene aliphatic group of frag. 2.

Comparison of dimer formation energies in toluene and in vacuum shows that in general the solvent has little effects to destabilize the dimers with respect to the monomers; *i.e.*, the dimerization energy becomes less negative (the differences are + 0.92 for 2-AEPip, + 0.13 for 3-APMo and +0.23 kcal/mol for DMPA dimer 1). The exception is DMPA dimer 2, in which ΔE_{dim} becomes slightly more negative (-0.09 kcal/mol).

The most stable dimers with respect to the monomers are those of 2-AEPip and DMPA; the dimer of 3-APMo is also stable, but its dimerization energy is relatively low. This indicates that the two former molecules have a much greater probability of being available as dimers in solution than 3-APMo has; these results are consistent with the the experimental kinetics results [13, 40, 41]. It has been pointed out that in diamines the presence of an intramolecular hydrogen bond prevents or significantly reduces the formation of intermolecular H-bonded aggregates. From the present results, we can see that the strongest intermolecular H-bonded dimer correspond to 2-AEPip. The next dimers, in order of stability, are DMPA 1, DMPA 2 and 2-APMo. Note that in DMPA 1 and 2-APMo, one of the monomer´s intramolecular H-bond is broken to establish the dimer´s intermolecular H-bond, whereas in DMPA 2 both intramolecular H-bonds are broken to form the dimer. Also note that this last conformer is the only one that becomes more stable by the solvent interaction.

Additionally, we estimated the dimerization constants at room temperature considering the 0 K dimerization energies (*i.e.*, the entropy contribution is neglected). We find that for 2-AEPip it is approximately nine times higher than the corresponding value for the most stable DMPA dimer found (DMPA 1).

Table 4 shows the BSSE (in a.u.) calculated for the dimers in vacuum and in toluene. Comparison between both cases shows that the contribution of BSSE in solution varies from -11% to a +55% respect to the vacuum value. In solution the BSSE has an appreciable contribution to the dimer formation energy representing 16% to 69% of its uncorrected value.

Considering that the previously described DFT calculations concerns to properties at 0 K, we end this section with a comment on molecular dynamic (MD) simulations exploring the temperature effects on the stabilibity of dimers for the studied diamines. We consider the time evolution of an isolated dimer by performing MD simulations using the AM1 method at 300 K. Consistent with the higher dimerization energy found for 2-AEPip at 0 K, preliminary results show that this molecule keeps its dimer configuration for a relatively longer time compared to DMPA and 3-APMo, which soon after less than one psec. dissociate into their corresponding monomers. More research in this line work would be desirable to evaluate explicitly the temperature effects on the stability of amine´s dimers.

Table 4: BSSE for 2-AEPip, 3-APMo and DMPA dimers calculated in vacuum and in toluene.

	Vacuum (au)	**Toluene (au)**
2-AEPip	0.633	0.566
3-APMo	0.689	0.633
DMPA 1	0.589	0.912
DMPA 2	0.710	0.819

CONCLUSIONS

In summary, we have investigated the molecular structure of 3-dimethylamino-l-propylamine (DMPA), 1-(2-aminoethyl)-piperidine (2-AEPip) and 3-(aminopropyl)-morpholine (3-APMo) in order to analyze nucleophile structural effects and self-aggregation states by H-bonding and correlate with kinetic results in ANS reactions. The theoretical calculations were made using Austin Method 1 and further *ab initio* optimizations using the Density Functional Theory, the diffuse atomic orbital basis set 6-31++G(d) and the hybrid exchange-correlation functional B3LYP. To study the role of solvent in the formation and stabilization of H-bonds in the cited diamines, we applied the continuum solvent model while simultaneously correcting for basis set superposition errors using the Counterpoise method. We found that the BSSE represents an important contribution to the dimer formation energy, of up to 69% of its uncorrected value, and cannot be neglected. In all cases, solvation stabilizes the monomers; all dimers are stable in toluene but only conformer 2 of DMPA, is more stable with respect to vaccum.

From the present results, it follows that the strongest intermolecular H-bonded dimer is 2-AEPip, for which there is no intramolecular H-bond formed within the monomers. The next dimers, in order of stability, are DMPA conformers and finally, 3-APMo. The present theoretical results are in line with ANS experimental studies, and they clearly provide additional support to the role of homo-dimer diamine nucleophile formation in aprotic solvents.

Acknowledgements. The authors thank Dr. Marshall D. Newton for the details and suggestions about using the Counterpoise method with the PCM model. We also gratefully acknowledge financial support from the Universidad Nacional del Comahue (grant Nº I157-UNCo, I183-UNCo) and from the Agency for the Promotion of Science and Technological Research (ANPCYT) from Argentine (grant n° PICT 2007/0347).

REFERENCES

[1] a) R. F. Ribeiro, A. V. Marenich, C. J. Cramer, D. G. Truhlar, *Phys. Chem. Chem. Phys.* **2011**, *13*, 10908. b) S. Scheiner, *Hydrogen Bonding: A Theoretical Perspective*, Ed. Oxford University Press, New York, 1997.

[2] G. R. Desiraju, T. Steiner, *The Weak Hydrogen Bond in Structural Chemistry and Biology*, Ed. Oxford University Press Inc., New York, 1999.

[3] a) G. A. Jeffrey, *An Introduction to Hydrogen Bonding*, Ed. Oxford University Press, New York, 1997. b) G. A. Jeffrey, W. Saenger, *Hydrogen Bonding in Biological Structures*, Ed. Springer-Verlag, Berlin, 1991.

[4] a) M. Solimannejad, S. Scheiner, *Chem. Phys. Lett.*, **2006**, *424*, 1. b) Vančo Kočevski, Ljupčo Pejov, *J. Phys. Chem. A,* **2010**, *114*, 4354.

[5] a) S. J. Grabowski, A. Pfitzner, M. Zabel, A. T. Dubis, M. Palusiak, *J. Phys. Chem. B,* **2004**, *108*, 1831. b) S. J.Grabowski, *J. Phys. Chem. A,* **2007**, *111*, 3387.

[6] C. Boga, L. Forlani, *J. Chem. Soc. Perkin Trans.2,* **2001**, 1408.

[7] N. Sbarbati Nudelman, M. Marder, A. Gurevich, *J. Chem. Soc. Perkin Trans. 2,* **1993**, 229.

[8] a) E. D. Raczynska, M. Decouzon, J. F Gal, P. C. Maria, R. W Taft, F. Anvia, *J. Org. Chem.*, **2000**, *65* (15), 4635. b) E. D. Raczynska, K. Duczmal, M. Hallmann, *Trends in Org. Chem.,* **2008**, *12*, 85.

[9] a) N. S. Nudelman, *S_NAr Reactions of Amines in Aprotic Solvents* in: S. Patai, (Ed.) *The Chemistry of Amino, Nitroso, Nitro and Related Groups*, Wiley, Chichester, 1996, pp 1215-1300. b) N. S. Nudelman, C. E. S. Alvaro, J. S. Yankelevich, *J. Chem. Soc. Perkin Trans.2,* **1997**, 2125 and references cited therein.

[10] F. Bergero, C. E. S. Alvaro, N. S. Nudelman, S. Ramos de Debiaggi, *J. Mol. Struct. (Theochem,),* **2009**, *896*, 18.

[11] A. V. Marenich, C. J. Cramer, D. J. Truhlar, *J. Chem. Theory Comput.*, **2010**, *6*, 2829.

[12] a) D. G. Liakos, A. Hansen, F. Neese, *J. Chem. Theory Comput.,* **2011**, *7*, 76. b) J. Řezáč, P. Hobza, *J. Chem. Theory Comput.*, **2012**, *8*, 141.

[13] C. E. S. Alvaro, A. D. Ayala, N. S. Nudelman, *J. Phys. Org. Chem.*, **2011**, *24* (2) 101.

[14] Z. Liu, R. C. Remsing, D. Liu, G. Moyna,V. Pophristic, *J. Phys. Chem., B* **2009**, *113* (20), 7041.

[15] R. G. Parr, D. Yang, Density-Functional Theory of Atoms and Molecules, Ed. Oxford University Press, New York, 1989, Ch. 3.

[16] a) M. Korth, M. Pitonák, J. Rezác, P. Hobza, *J. Chem. Theory Comput.*, **2010**, *6*, 344. b) K. E. Riley, M. Pitoňák, J. Černý, P. Hobza, *J. Chem. Theory Comput.*, **2010**, *6*, 66. c) J. Rezác, P. Hobza, *J. Chem. Theory Comput.*, **2012**, *8* (1), 141. d) A. Krishtal, D. Geldof, K. Vanommeslaeghe, C. Van Alsenoy, P. Geerlings, *J. Chem. Theory Comput.*, **2012**, *8*, 125.

[17] C. N Rao, T. Pradeep, *Chem. Soc. Rev.*, **1991**, *20*, 477.

[18] C. E. S. Alvaro, N. S. Nudelman, *Arkivoc,* **2003**, *X*, 95.

[19] C. E. S. Alvaro, N. S. Nudelman, *J. Phys. Org. Chem.*, **2005**, *18*, 880.

[20] F. Ramondo, L. Bencivenni, *J. Chem. Soc. Perkin Trans.2,* **1995**, 1797.

[21] N. S. Nudelman, C. E. S. Alvaro, *J. Phys. Org. Chem.,* **2011**, *24* (11), 1067.

[22] C. E. S. Alvaro, N. S. Nudelman, *Int. J. Chem. Kinet.,* **2010**, *42* (12), 735.

[23] F. B. Van Duijneveldt, J. G. C. M van Duijneveldt-van de Rijdt, J. H. van Lenthe, *Chem. Rev*., **1994**, *94* (7), 1873.

[24] Gaussian 09, Revision A.1, Gaussian, Inc., Wallingford CT, 2009. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr. J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, N. J. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox.

[25] M. S. J. Dewar, E. G. Zoebisch, R. F. Healy, J. P. Stewart, *J. Am. Chem. Soc.,* **1985**, *107*, 3902.

[26] a) A. D. Becke, *J. Chem. Phys.* **1993**, *98* (7), 5648. b) C. Lee, C. W. Yang, R. G. Parr, *Phys. Rev., B* **1988**, *37*, 785.

[27] L. González, O. Mó, M. Yañez, J. Elguero, *J. Mol. Struct. (Theochem),* **1996**, *371*, 1.

[28] L. González, O. Mó, M. Yañez, *J. Phys. Chem., A,* **1997**, *101*, 9710.

[29] L. González, O. Mó, M. Yañez, *J. Chem. Phys.*, **1998**, *109*, 139.

[30] M. Luzynski, D. Rusinska-Poszak, H. G. Mack, *J. Phys. Chem. A,* **1997**, *101*, 1542.

[31] M. Luzynski, D. Rusinska-Poszak, H. G. Mack, *J. Phys. Chem. A*, **1998**, *102*, 2899.

[32] L. González, O. Mó, M. Yañez, *J. Org. Chem.* , **1999**, *64,* 2314.

[33] J. Tomasi, B. Mennucci, R. Cammi, *Chem. Rev.*, **2005**, *105*, 2999.

[34] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B,* **2009**, *113*, 6378.

[35] Q. Wang, M. D. Newton, *J. Phys. Chem. B,* **2008**, *112*, 568.

[36] R. F. W. Bader, *Chem. Rev.*, **1991**, *91*, 893.

[37] F. Biegler-König, J. Schönbohm, D. Bayles, AIM2000, *J. Comp. Chem.,* **2001**, *22* 545.

[38] R. Parthasarathi, V. Subramanian, N. Sathyamurthy, *J. Phys. Chem. A*, **2006**, *110*, 3349.

[39] C. F. Matta, J. Hernandez-Trujillo, T. Tang, R. W. Bader, *Chem. Eur. J.*, **2003**, *9*, 1940.

[40] C. E. S. Alvaro, N. S. Nudelman, *Trends in Org. Chem.*, **2011**, *15*, 95.

[41] C. E. S. Alvaro, N. S. Nudelman, *Phys. Chem.*, **2013**, *3*(2), 39.