Special issue article

Journal of Physical Organic Chemistry

Received: 24 August 2015, Revised: 17 October 2015, Accepted: 2 November 2015,

(wileyonlinelibrary.com) DOI: 10.1002/poc.3519

Aromatic nucleophilic substitution in aprotic solvents using hydrogen-bonded biological amines. Kinetic studies and quantum chemical calculations

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Intermolecular and intramolecular non-bonding interactions play a crucial role in determining physical and biological properties of relevant amines, and we have recently reported that they are also responsible for changing mechanisms in aromatic nucleophilic substitution (ANS) involving amine nucleophiles, when they are carried out in solvents of low permittivity. The present work describes ANS in toluene with a series of biological amines that can set specific hydrogen bonding (H bonding) interactions due to their special molecular structures. Kinetic studies of ANS with 2-amino-5-guanidinopentanoic acid (arginine), (4-aminobutyl)guanidine (agmatine), 2,6-diaminohexanoic acid (lysine) and 3,4-dihydroxyphenethylamine (dopamine) towards 1-chloro-2,4-dinitrobenzene in toluene are reported. The kinetic results are compared with those obtained with 2-guanidinobenzimidazole and 2-(1H-imidazole-4-yl)ethanamine (histamine); both amines form intramolecular H bonds. The special types of H bonding were also investigated by *ab initio* density functional theory calculations, at the B3LYP/6-31++G(d,p) level, including counterpoise corrections to account for basis set superposition errors and solvent effects at the polarized continuum model level. Copyright © 2015 John Wiley & Sons, Ltd.

Keywords: aprotic solvents; aromatic nucleophilic substitution; biological amines; dimer nucleophile mechanism; hydrogen bonding

INTRODUCTION

The crucial role that intermolecular and intramolecular non-bonding interactions play in the physical and biological properties of relevant amines is a subject of active experimental[1,2] and theoretical[1,3] research at present. In fact, the novel definition for hydrogen bond (H bond) recommended by the IUPAC takes into account the theoretical and experimental knowledge acquired over the last decades.[4] On the other hand, we have recently reported the influence of H bonding in changing mechanisms of aromatic nucleophilic substitutions (ANS) involving amine nucleophiles, when they are carried out in solvents of low permittivity[5,6] and determined by NMR measurements the degree of H bonding for those amines in each case.[7] In the very well-known two-step addition–elimination mechanism for ANS,[8,9] in the first step, the nucleophile attacks the *ipso* position corresponding to the leaving group in aromatic ring with electron-withdrawing groups to yield a zwitterionic σ intermediate that contains an acidic proton; in the second step, the proton is removed by a base, usually the nucleophile itself.

Nowadays, there are abundant literature reports about ANS studies referred to elucidate the factors that influence the reactivity in ANS and its many applications in organic chemistry, biochemistry and industrial processes. To cite some of the more recent, it has been reported the arylation of heteroatom nucleophiles by using activated haloarenes, with or without metal catalysts,[10] while experimental and computational studies have been carried out on the factors determining the leaving group ability,[11] the preferential solvation[1] and the reactivity indices profile[12] as a tool for the analysis of reaction mechanisms in activated ANS. Furthermore, it is worth mentioning the importance of ANS in sustainable chemistry, including a treatment of halohydrocarbons and polychlorinated biphenyls for the decontamination of groundwater[13] and the elimination of chlorine in the synthesis of 4-aminodiphenylamine.[14]

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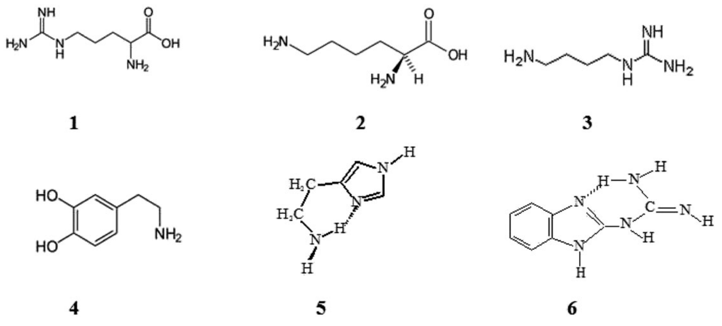
In the last decades, there were major developments that led to an improved understanding of the factors governing the addition–elimination pathway, and a new mechanism, called the *dimer nucleophile*, was found for activated ANS with amines in solvents of low permittivity, where *a third order* in amine concentration giving an overall *fourth-order* kinetics was determined.[6,15] Early works providing kinetic,[16] conformational[17] and thermodynamic[18] evidence for the *dimer nucleophile* mechanism, as well as some *ab initio* calculations,[6] were performed in several ANS with nitro-activated substrates and poor leaving groups, for which the second step is rate-determining. More recently, we published atypical findings in ANS with amines that were purposefully selected because of their special structures, which are able to form intramolecular or intermolecular H bonds, such as alicyclic and aliphatic diamines and polyamines.[5,19] These studies, carried out in pure as well as in binary mixtures of aprotic solvents, were performed with substrates where the *first step* is rate-determining. The obtained results are interpreted by the *dimer nucleophile mechanism*,[18] which involves the attack of the amine hydrogen-bonded dimer reacting with the substrate in the first step, superimposed to the classical attack by the monomer. This behaviour was fully confirmed by abundant evidence from several different approaches.[15,20,21]

With the aim of broadening the range of ANS where H bonding could play a significant role, the present work reports kinetic results using monofunctional and polyfunctional amines of significant importance in biological systems. Kinetics studies were performed using 2,4-dinitrochlorobenzene (DNClB) as the substrate in ANS in toluene with the following amines: 2-amino-5-guanidinopentanoic acid (arginine), (4-aminobutyl)guanidine (agmatine), 2,6-diaminohexanoic acid (lysine), 2-guanidinobenzimidazole (2-GB), 2-(1H-imidazole-4-yl)ethanamine (histamine) and 3,4-dihydroxyphenethylamine (dopamine). For these amines, intramolecular and/or intermolecular H bonds could occur; the structures are depicted in Scheme 1.

To provide valuable insight into the predominant type of H bond formed, we performed *ab initio* density functional theory (DFT)[22] calculations on the aforementioned amines determining their optimal geometry in vacuum and in toluene for monomers and dimers, H bonds formation and dimerization energies, at the B3LYP/6-31++G(d,p) level.[23] Theoretical studies based on *ab initio* DFT[24] methods currently provide information about electrostatic, polarizability, strength and charge transfer components of H bonding that contribute to the geometrical and chemical behaviour.[3] To simultaneously evaluate counterpoise corrections to account for basis set superposition errors (BSSE) and solvent effects, we implemented a methodology that was previously described in detail.[25]



Scheme 1. Molecular structure of (1) arginine, (2) lysine, (3) agmatine, (4) dopamine, (5) histamine and (6) 2-guanidinobenzimidazole

EXPERIMENTAL

Reagents and solvents

All solvents and reagents were analytical reagent grade and were purified using previously reported procedures.19a

2-Amino-5-guanidinopentanoic acid (arginine, Merck, Kenilworth, NJ, USA): the commercial product was crystallized from absolute ethanol (mp. 240 °C,[26] 244 °C); the procedure was repeated until no impurities were detected by thin-layer chromatography.

For the following amines, 1-(4-aminobutyl)guanidine (agmatine, Sigma-Aldrich, St. Louis, MO, USA), 4-(2-aminoethyl)benzene-1,2, diol (dopamine, Merck), 2,6-diaminohexanoic acid (lysine, Sigma-Aldrich) and 2-(1H-imidazole-4-yl)ethanamine (histamine base, Fluka), the commercial products were used without further purification.

All the previous amines were kept in a desiccator protected from light, prior to use.

2-Guanidinobenzimidazole (Sigma-Aldrich) was crystallized twice from ethyl acetate. To assure full removal of the solvent, the crystals were dissolved in chloroform, and vacuum was applied until a dried residue was obtained; it was reduced to powder in a mortar, and the procedure was repeated until no impurities were detected by thin-layer chromatography. Finally, it was kept in a desiccator protected from light under dry nitrogen atmosphere (mp. 242–244 °C,[27] 242.8–244.5 °C).

2,4-Dinitrochlorobenzene (Sigma-Aldrich) was crystallized twice from absolute ethanol (mp. 52–53 °C,19a 52–53 °C).

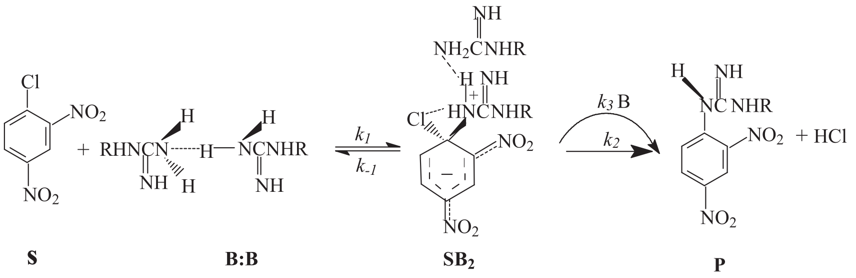
Each one of the ANS products was prepared from DNClB and the corresponding amine following the procedure previously described.[16] Schematic structure of substitution products is shown in Scheme 2.

Spectrophotometric measurements and kinetic procedures

UV–Vis spectra of the substrates, the products and different mixtures of both compounds with the amine in toluene at several concentrations were recorded in a Shimadzu (Kyoto, Japan) UV–Vis 240 graphic printer PR-1 spectrophotometer. The extinction coefficients of the products were determined at $\lambda = 420$ nm and at $\lambda = 460$ nm. At those wavelengths, the reagents are transparent. All the solutions were found to obey Beer's law.

Kinetic runs were performed by the methods previously reported[19,28] following the appearance of the reaction product at $\lambda = 420$ or 460 nm.

The reactions of DNClB with arginine, agmatine, lysine and dopamine were recorded directly in the thermostated cell of the spectrophotometer at 25 ± 0.2 °C. The reactions with histamine and 2-GB were carried out in sealed ampoules (under nitrogen) at 40 ± 0.2 °C. In all cases, pseudo-first-order rate kinetics were observed. The absorption spectrum of the reaction mixture at 'infinite time' corresponded within ±2% with the 'theoretical' value calculated from application of Beer's law to solutions of the product independently prepared in toluene. Pseudo-first-order coefficients, k_Ψ, were obtained by the least-squared method as the slope of the correlation ln $(A_\infty - A_t)/A_\infty$ against time, where A_∞ is the optical density of the



Scheme 2. Schematic aromatic nucleophilic substitution reaction by the 'dimer nucleophile mechanism'

reaction mixture measured at infinite time (more than 10 half-lives). No corrections for expansion coefficients were applied to the concentration values.

COMPUTATIONAL PROCEDURES

Energy and geometry of molecules in vacuum and in solution

Calculations were performed using Gaussian 09.[29] The semiempirical method AM1[30] was used with a Monte Carlo algorithm for an automatic search of equilibrium conformers of monomers and dimers. A selection of these conformers was further optimized using DFT[22] with the 6-31++G(d,p) basis set[31] and the hybrid exchange–correlation functional B3LYP,[23] with the software's 'tight' convergence criteria for energy and geometry. All optimized geometries, in vacuum and in solution, were confirmed to be potential energy minima by computing vibrational frequencies. For dimers in vacuum, the BSSE was corrected with the counterpoise method[32] as implemented in the software. This level of calculation has shown to provide reliable structural and energetic information on both intramolecular and intermolecular hydrogen bonds in good agreement with higher-level *ab initio* calculations.[33–38] Solvent effects were accounted for by geometry optimizations with the integral equation formalism variant[39] of the polarized continuum model. Because the software does not perform geometry optimizations with solute electron density (SMD),[40] the final energy was recalculated using the self-consistent solvation model based on SMD, which includes non-electrostatic energy terms, and it is the recommended model for computing solvation energies.[29] To evaluate the BSSE correction for the dimers in solution, the counterpoise procedure was applied 'manually' as described in our previous work.[25]

Hydrogen bond search and characterization

The presence of intramolecular and intermolecular hydrogen bonds, including non-conventional H bonds,[41] was studied using the Atoms in Molecules (AIM) theory[42] with the multiWFN software.[43] 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 H bonds have been found to be roughly proportional to the bond's stabilization energy.[44] The positive sign of the Laplacian found in all H bonds also shows their closed-shell (non-covalent) nature.[42] The ellipticity ε at the BCP shows the electron density's deviation from circular symmetry: $\varepsilon = 0$ indicates a perfect symmetric bond, that is, a σ bond type, and $\varepsilon = 1$ indicates a π bond. Higher values of ε are indicative of a strained bond in a ring structure, which is about to be broken.[42]

RESULTS AND DISCUSSION

Reactions of DNClB with arginine, agmatine, lysine and dopamine in toluene

Intermolecular and intramolecular H bonds are one of the principal types of non-covalent interactions that have crucial impact on the molecular structure and reactivity of organic and biological compounds.[1–3] A recent definition by the IUPAC considers that H bond is an interaction between a hydrogen atom from a molecule or a molecular fragment X–H in which X is more electronegative than H, and an atom or a group of atoms in the same or a different molecule, in which there is evidence of bond formation.[4] Self-association of amines to form mainly dimers by H bonds is a long-known phenomenon, and there is abundant information in the literature about dimers that are responsible for the 'dimer nucleophile' mechanism when amines are used in ANS carried out in aprotic solvents.[5,6] Intermolecular hydrogen bonding increases the nucleophilicity of the dimer compared with the monomer, as confirmed by semi-empirical[45] and *ab initio* calculations.[24]

On the other hand, when two amino groups are in a rigid appropriate geometry, strong intramolecular H bonding is easily established, and such compounds exhibit unusually high basicity.[45] Intramolecular H bonding in the nucleophile also causes an increase in its nucleophilicity, as it was formerly demonstrated in kinetic studies of ANS with *cis*- and *trans*-1,2-diaminocyclohexane.[17] Moreover, the leaving group ability in activated ANS was recently revised, and the authors found that the leaving group order in gas phase is or would be dependent on the exact combination of nucleophile, leaving group and substrate framework. The geometry of the ANS transition state permits useful, qualitative conceptual distinctions to be made between this type of reaction and other modes of nucleophilic attack.[11] The authors report computational studies of the reaction of piperidine and dimethylamine with the aryl halides using methanol as solvent; the results indicate that polarizability, solvation and negative hyperconjugative effects are all relevant in producing the element effect in methanol.[11]

The present work reports kinetic results using monofunctional and polyfunctional biological amines that were selected due to their special structures that allow the formation of intramolecular or intermolecular homo-dimers by H bonds. The reactions of DNClB with each one of the amine depicted in Scheme 1 were carried out in toluene in the presence of variable amounts of the nucleophile. The rate behaviour is compared with previous kinetic results obtained with 2-(1H-imidazole-4-yl)ethanamine (histamine).[5]

Table 1 gathers the results: the bimolecular rate coefficient k_A and the ratio k_A/[B] are given. For arginine, agmatine, lysine and dopamine, the second-order rate coefficients, k_A, were found to increase rapidly with the amine concentration, [B]; the plot of k_A versus [B] (Figs 1 and 2) illustrates a quadratic dependence, whereas the plot of k_A/[B] versus [B] is a straight line as shown in Figs 3 and 4. These results are consistent with a

Table 1. Reaction of 2,4-dinitrochlorobenzene, DNClB[a,b], with arginine, agmatine, lysine, dopamine, histamine and 2-GB in toluene at 25 and 40 ± 0.2 °C

10^2 [Arginine],[a] M	0.58	0.71	0.83	1.08	1.32	1.80	2.13	2.54	2.80	3.20
k_A, $s^{-1}\,M^{-1}$	1.40	2.32	3.04	5.28	8.50	15.0	20.9	28.9	33.9	43.9
10^{-2} k_A/[B], $s^{-1}\,M^{-2}$	2.41	3.27	3.66	4.89	6.44	8.33	9.81	11.4	12.1	13.7
10^2 [Agmatine],[a] M	0.42	0.65	0.80	0.96	1.25	1.40	1.84	2.30	2.75	3.10
10^4 k_A, $s^{-1}\,M^{-1}$	0.55	1.28	1.48	2.35	4.00	4.50	6.90	10.8	13.9	18.3
10^2 k_A/[B], $s^{-1}\,M^{-2}$	1.30	1.97	1.85	2.46	3.20	3.21	3.75	4.70	5.05	5.90
10^2 [Lysine],[a] M	0.25	0.50	0.70	0.90	1.20	1.50	1.85	2.20	2.50	2.90
10^3 k_A, $s^{-1}\,M^{-1}$	1.49	3.20	4.60	6.20	9.10	12.6	17.8	21.5	25.4	34.9
10 k_A/[B], $s^{-1}\,M^{-2}$	5.96	6.40	6.57	6.89	7.58	8.40	9.08	9.77	10.2	12.3
[Dopamine],[a] M	0.05	0.11	0.20	0.30	0.40	0.55	0.70	0.80	0.90	1.20
10 k_A, $s^{-1}\,M^{-1}$	0.58	1.35	2.78	4.60	6.89	10.9	14.3	17.9	21.8	33.9
10 k_A/[B], $s^{-1}\,M^{-2}$	11.6	12.3	13.9	15.3	17.2	19.8	20.5	22.4	24.2	28.2
[Histamine],[b,c] M	0.25	0.50	0.70	0.90	1.20	1.50	1.85	2.10	—	—
10^5 k_A, $s^{-1}\,M^{-1}$	1.20	3.90	5.60	7.20	9.30	10.6	12.8	15.5	—	—
10^2 [2-GB],[b] M	0.25	0.50	0.70	0.90	1.21	1.51	1.85	2.10	2.50	—
10^6 k_A, $s^{-1}\,M^{-1}$	1.88	4.30	6.00	7.55	10.1	11.3	13.9	16.8	19.6	—

2-GB, 2-guanidinobenzimidazole. Second-order (k_A) and third-order (k_A/[B]) rate coefficients.
[a][DNClB] = 5.0×10^{-4}M; 25 ± 0.2 °C.
[b][DNClB] = 5.12×10^{-4}M; 40 ± 0.2 °C.
[c]Data from Ref. .[5]

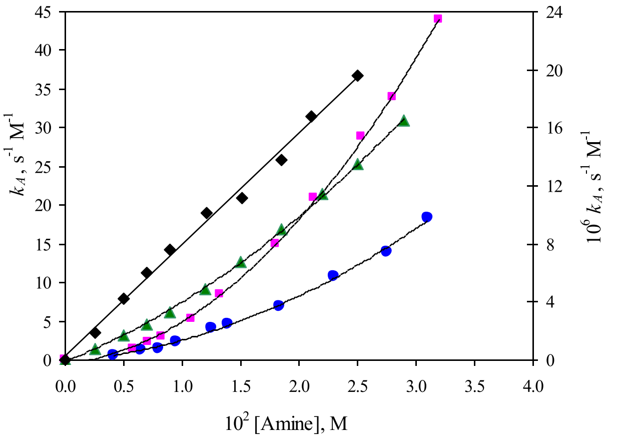


Figure 1. Second-order rate coefficients, k_A, for the reactions of 2,4-dinitrochlorobenzene, with ■ arginine[a] (left *Y*-axis scale), ▲ lysine[a] (10^3 left *Y*-axis scale), ● agmatine[a] (10^4 left *Y*-axis scale) and ◆ 2-guanidinobenzimidazole[b] (10^6 right *Y*-axis scale), in toluene at 25.0[a] and 40.0[b] ± 0.2 °C, respectively, as a function of amine

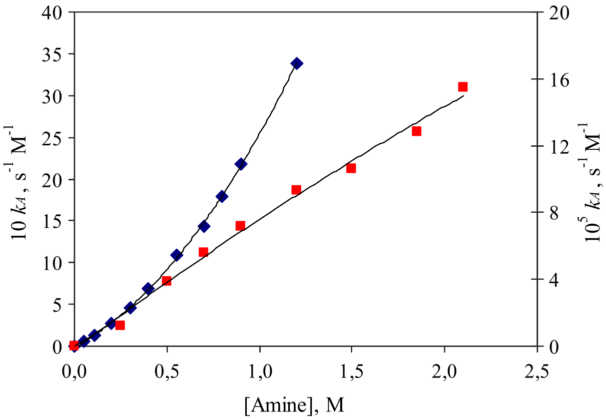


Figure 2. Second-order rate coefficients, k_A, for the reactions of 2,4-dinitrochlorobenzene with ◆ dopamine[a] (left *Y*-axis scale) and ■ histamine[b] (right *Y*-axis scale) in toluene at 25.0[a] and 40.0[b] ± 0.2 °C as a function of amine

third-order-in-amine term in the kinetic law, confirming the presence of a dimer acting as a nucleophilic entity, as shown by Scheme 2. The proposed reaction pathway imply that the dimer of the nucleophile (B : B) attacks the substrate, S, forming the intermediate, SB_2, and the third molecule of amine assists the decomposition step. Both transition states in Scheme 2 are highly zwitterionic, and the extra amine molecule should help to stabilize the developing charges in non-polar solvents. The third molecule of amine would form the acid conjugate of the dimer through concerted detachment of the proton from the intermediate. The *protonated dimer* catalyses the nucleofuge departure in low-permittivity solvents.[6]

For arginine and agmatine, the intercept in Fig. 3 is null, indicating that these reactions proceed fully by the 'dimer nucleophile' mechanism.[15] By the contrary, the intercept for lysine and dopamine is non-zero (Figs 3 and 4), allowing to infer that classical and dimer mechanisms take place in the global reaction. With chlorine as the nucleofuge, usually the first step is rate-determining; nevertheless, a third-order-in-amine kinetic law was observed, as it has been recently reported using alicyclic diamines and polyamines that form intramolecular or intermolecular hydrogen bond in aprotic solvents.[6,8,20,21] As shown in Table 1, the reactions with histamine and 2-GB are the slower ones, reflecting the effects of sterically demanding polyamines for reacting with the substrate; in contrast, the flexible structure polyamines that form intermolecular homo-dimers have the nucleophilic atom more available and form stable dimers (see theoretical calculations), leading to faster reactions.

These results allow to conclude that under the conditions of the present study, amine dimers are formed and react as better nucleophiles compared with amine monomers.

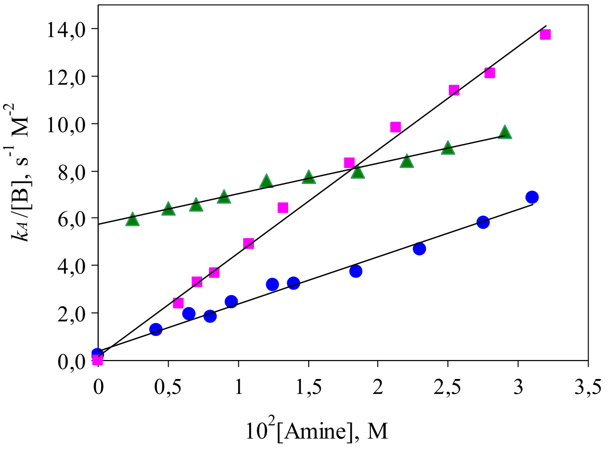


Figure 3. Third-order rate coefficient, k_A/[B], for the reactions of 2,4-dinitrochlorobenzene with ■ arginine (10^{-2} k_A/[B]), ▲ lysine (10 k_A/[B]) and ● agmatine (10^2 k_A/[B]) in toluene at 25.0 ± 0.2 °C as a function of amine

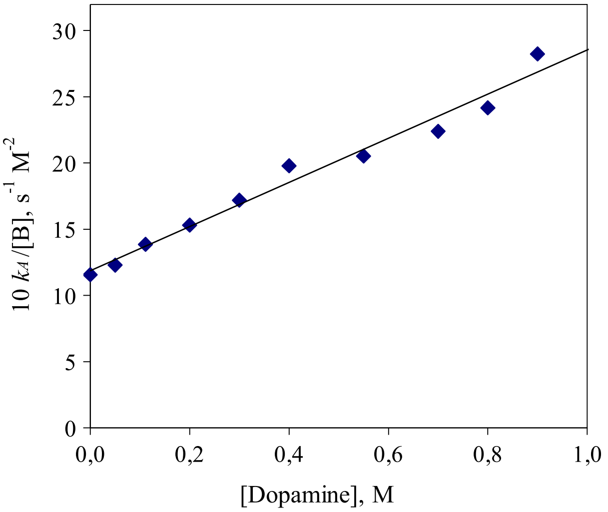


Figure 4. Third-order rate coefficient, k_A/[B], for the reactions of 2,4-dinitrochlorobenzene with dopamine in toluene at 25.0 ± 0.2 °C as a function of amine

Reactions of DNClB with histamine and 2-GB in toluene

In order to examine the interpretation that the intermolecular H bonds in arginine, agmatine, lysine and dopamine are responsible for the observed results, the reactions of nucleophiles that are able to form intramolecular H bonding were studied using the same substrate. The polyamines chosen for this purpose were 2-guanidinobenzimidazole (2-GB) and 2-(1H-imidazole-4-yl)ethanamine (histamine).[5] Addressing the different reactivity of the amines studied, the kinetics of the reactions with arginine, agmatine, lysine and dopamine were performed at 25 ± 0.2 °C, and the reactions with histamine and 2-GB were carried out at 40 ± 0.2 °C. The second-order rate coefficient, k_A, are given in Table 1. As shown in Figs 1 and 2, k_A increases steadily for both nucleophiles; the plot of k_A versus [B] is a straight line with zero intercept and a correlation coefficient, $R^2 = 0.991$ for histamine and $R^2 = 0.994$ for 2-GB.

For these two amines, intramolecular hydrogen bonds are easily established because their rigid geometries prevent or diminish the intermolecular dimer formation; the classical mechanism of base-catalysed decomposition of the zwitterionic intermediate, SB, is obeyed. The null intercept indicates that the spontaneous decomposition of SB is negligible. The kinetic results obtained are interpreted as an 'atypical' base-catalysed decomposition of the zwitterionic intermediate derived from an *intramolecular dimer*.

Intramolecular H bond in 2-GB and histamine plays an important role in stabilizing the molecules, because a pseudo-six-membered ring is formed between the nitrogen of the guanidine group and the benzimidazole in 2-GB,[46] while in histamine, the H bond is between the nitrogen of the aliphatic chain and the imidazole nitrogen.

Few years ago, Babatunde *et al*. studied the kinetics of reactions of 2,4,6-trinitrochlorobenzene and phenyl-2,4.dinitrophenylether with some primary amines in toluene[47] and phenyl-2,4,6-trinitrophenyl ether with 1,2-diaminobenzenes and 1,4-diaminobenzenes,[48] and with both substrates in binary solvents.[49] The authors compare 1,2-diaminobenzenes and 1,4-diaminobenzenes to establish if intramolecular H bonding is important: they observed a third order in amine for the reactions with 1,4-diaminobenzene, while the reactions with the 1,2-isomer show second-order dependence on amine concentration. In fact, they mimic a system similar to one using 1,2-diaminocyclohexane and 1,4-diaminocyclohexane as nucleophiles that we studied several years ago to provide a new 'conformational' evidence for the dimer nucleophile.[17] Although the authors rationalized their results in terms of a strained six-membered cyclic transition state mechanism, those can be easily interpreted by the dimer nucleophile mechanism. In 1,2-diaminobenzene, intramolecular H bond prevents the intermolecular H-bonded dimer, while in the reactions carried out in aprotic–protic solvents, the formation of nucleophile/co-solvent, mixed aggregates prevents the H bond self-aggregation of the nucleophile, as we previously reported.[17–19] Preferential solvation can be responsible for dramatic changes in reaction mechanisms in ANS, as it has been shown experimentally[6,8,18] and recently confirmed by quantum chemical calculations.[1] Previous works reported by Hirst *et al.*[50] proposed that the upward curving plots observed in ANS reactions carried out in aprotic solvents can be explained via cyclic transition state formation and electrophilic catalysis expulsion of the leaving group by homo-(or hetero)conjugated acid of the nucleophile by proton transfer from the intermediate. Hirst's interpretation is common to dimer mechanism, reflecting different parts of a spectrum of methods for the formation of the intermediate.[6] For a given nucleophile, dimer formation increases with increases of concentration and hence increases the reaction rate as observed in the present study.

Quantum chemical calculation results

Noncovalent interactions are very sensitive to geometric parameters, and their strengths can often vary significantly by small geometric perturbations. This sensitivity contributes to the geometrical and chemical behaviour, especially in the case of strong H bonds.[51] In the present section, the results obtained by the *ab initio* DFT methods, for the amines agmatine, arginine, dopamine, lysine, histamine and 2-GB, monomer and dimer structures, calculated in vacuum and in toluene, are discussed. In Table 2, we report the results obtained for the two amine monomers that show intramolecular hydrogen bonds in toluene. The solvation energies of the molecules (ΔE_{solv}) were calculated through the SMD energies, which include non-electrostatic

Table 2. Monomer solvation energy (in kcal mol^{-1}) and intramolecular H bond characteristics for histamine and 2-GB

Compound	ΔE_{solv}	H bond	d (Å)	α (°)	ρ (au)	$\nabla^2\rho$ (au)	ξ
Histamine	−9.52	N10…H–N1	2.45	129.0	0.011	0.037	0.09
2-GB	−16.6	N7…H–N13	1.93	132.3	0.032	0.092	0.03

2-GB, 2-guanidinobenzimidazole.

Table 3. Solvation and dimerization energies (in kcal mol^{-1}) and H bond characteristics for dimers of the amines studied in this work

Compound	ΔE_{solv}	ΔE_{dim}	Frag. 1	Frag. 2	d (Å)	α (°)	ρ (au)	$\nabla^2\rho$ (au)	ξ
Agmatine	−19.52	−4.85	N21–H…	…N39	1.98	177.1	0.029	0.068	0.08
			N16…	…H–N44	1.99	177.2	0.029	0.067	0.08
Arginine	−22.97	−47.55	N1–H…	…O50	1.74	174.7	0.041	0.113	0.04
			N5–H…	…O51	1.75	171.0	0.042	0.114	0.05
			N5–H…O25		1.86	160.5	0.030	0.092	0.06
				N31–H…O51	1.86	160.5	0.030	0.092	0.06
			O25…	…H–N31	1.75	171.0	0.042	0.114	0.05
			O24…	…H–N27	1.74	174.7	0.041	0.113	0.04
Dopamine	−15.25	−18.81		O32…H–O34	2.11	115.6	0.021	0.079	0.58
			N20…	…H–O32	1.69	170.9	0.056	0.102	0.01
			O10–H…	…N42	1.69	170.9	0.056	0.102	0.01
			O10…H–O12		2.11	115.6	0.021	0.079	0.58
Lysine	−12.69	−11.17	O22…	…H–O47	1.65	172.0	0.049	0.138	0.02
			O23–H…	…O46	1.65	174.1	0.049	0.139	0.02
			N1…	…H–N25	2.42	159.0	0.012	0.033	0.11

terms, evaluated in the integral equation formalism variant of the polarized continuum model geometries, minus the energies in vacuum, thus including geometric relaxation effects. In all cases, it is found, as expected, that solvation stabilizes the molecule. The H bond length d, the angle α and the bond's AIM characteristics, electron density, its Laplacian and the ellipticity at the BCP, are reported. Table 3 shows the dimer's properties for the most stable conformation found in toluene. The dimer's formation energies (ΔE_{dim}) and solvation energies (ΔE_{solv}) for the amine molecules are reported. In this case, ΔE_{dim} is referred to twice the energy of the monomer in solution. It is found that solvation energies are negative in all cases. The columns 'Frag. 1' and 'Frag. 2' show to which fragment the H-bonded atoms belong.

The corresponding structures in solution are shown in Figs 5–10.

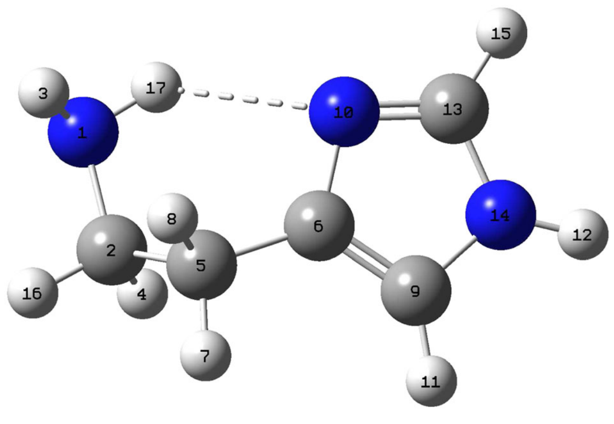


Figure 5. Structure and H bonding in histamine in toluene. C (grey); H (light grey); N (blue)

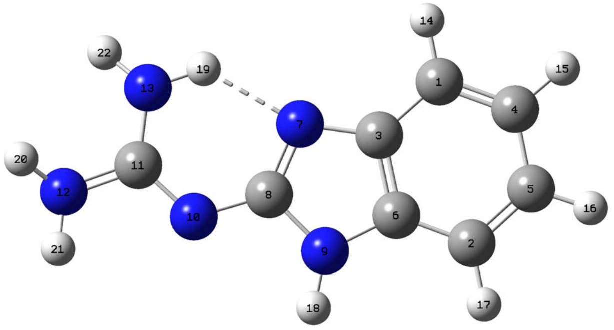


Figure 6. Structure and H bonding in 2-guanidinobenzimidazole in toluene. C (grey); H (light grey); N (blue)

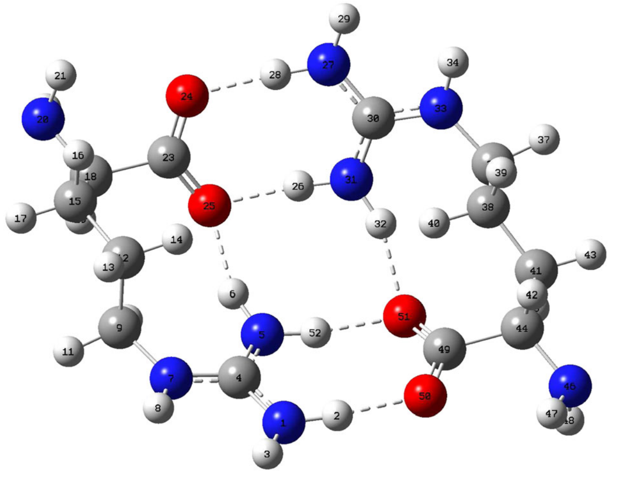


Figure 7. Structure and H bonding in arginine dimer in toluene. C (grey); H (light grey); N (blue); O (red)

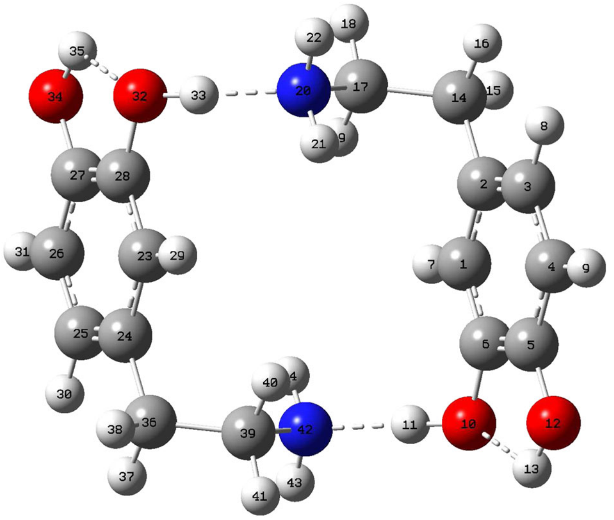


Figure 8. Structure and H bonding in dopamine dimer in toluene. C (grey); H (light grey); N (blue); O (red)

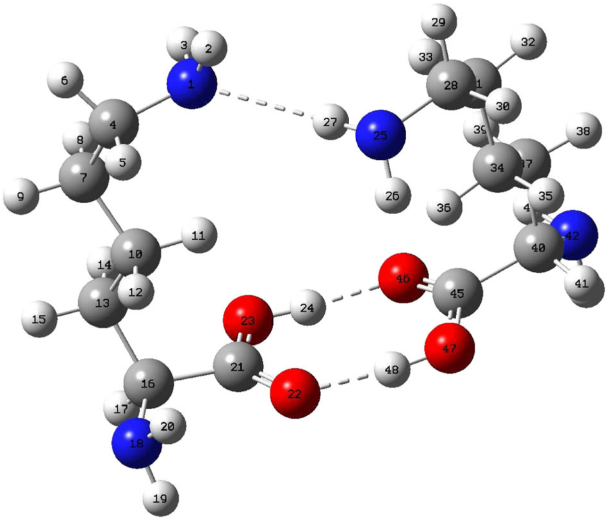


Figure 9. Structure and H bonding in lysine dimer in toluene. C (grey); H (light grey); N (blue); O (red)

It can be observed from these results that the most stable dimers correspond to those amines that have oxygen atoms enabling the formation of intramolecular and intermolecular H bonds of the type 'N–H…O' or 'N…H–O'. The highest values of ρ and $\nabla^2\rho$ were obtained for these 'mixed' H bonds, indicating that they are the strongest. Other non-conventional weak intramolecular H bonds of the type 'C–H…O' and/or 'C–H…H–N' were detected by the AIM methodology but are not shown.

The arginine's dimer is found to be the most stable one (Fig. 7) having four intermolecular and two intramolecular N–H…O bonds. Interestingly, the imine groups of one molecule are found to 'capture' the hydrogen of the –OH in the other molecule's COOH group, making the N atom act as a proton donor. The presence of these bonds is confirmed by the AIM theory, which reveals a covalent character of the N–H bonds and a closed-shell character of the H…O bonds. In dopamine, the second most stable dimer (Fig. 8), two intermolecular O–H…N bonds are found, and the two intramolecular O–H…O bonds are already present in the monomer.

Structure–reactivity relationship

Arginine and agmatine have a similar molecular structure: the first having a carboxyl group should reduce the amine reactivity and yet is much more reactive than agmatine; this is clear evidence of a very stable dimer formation, as shown by the calculations (Table 3). Lysine also has oxygen atoms but no imine groups; however, no H bonds of the type N–H…O were found. The dimerization energy lies between that of dopamine and 2-GB. The least stable homo-dimer is for agmatine; the intermolecular H bonds are formed between nitrogen atoms, similarly to intramolecular H bonds of histamine and 2-GB.

The calculation analysis can be resumed as follows: the increasing order in dimer's stability is correlated with the amine dimers that present H bonds involving oxygen atoms. In summary, theoretical results show that dimerization energy decreases in the order: arginine $\gg$ dopamine $>$ lysine $>$ agmatine $\cong$ histamine $\cong$ 2-GB (considering the intramolecular H bond for the last two molecules). The increasing order of dimer's stability correlates with the order of reactivity observed in the kinetic experiments, which indicate that arginine is the most reactive amine (as shown by Table 1).

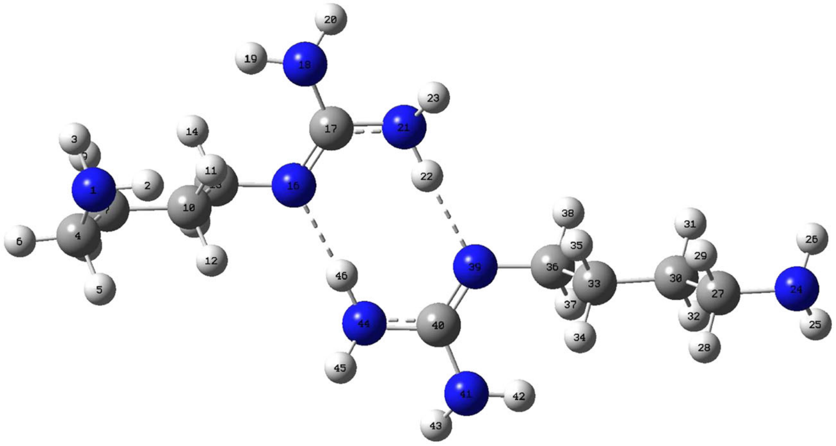


Figure 10. Structure and H bonding in agmatine dimer in toluene. C (grey); H (light grey); N (blue)

CONCLUSIONS

In the present work, we report kinetic and theoretical results using monofunctional and polyfunctional biological amines, which due to their particular structures allow the formation of intramolecular or intermolecular homo-dimers. Kinetic studies were performed in toluene with 2,4-dinitrochlorobenzene (DNClB) and the nucleophiles 2-amino-5-guanidinopentanoic acid (arginine), (4-aminobutyl)guanidine (agmatine), 2,6-diaminohexanoic acid (lysine) and 3,4-dihydroxyphenethylamine (dopamine). The kinetic results are compared with those obtained with 2-guanidinobenzimidazole (2-GB) and 2-(1H-imidazole-4-yl)ethanamine (histamine); because of their rigid molecular geometry, these two amines form intramolecular H bonds. The amines were also investigated by *ab initio* density functional theory calculations, at the B3LYP/6-31++G(d,p) level, including counterpoise corrections to account for basis set superposition errors (BSSE) and solvent effects at the polarized continuum model level. For monomers and dimers, the optimal geometry in vacuum and toluene, the predominant type of H bonds formation and their dimerization energies, were determined. The present study provides kinetic and theoretical evidence for ANS of biological amines in aprotic solvent that support that the *dimer nucleophile mechanism* is involved. This mechanism is based on the strong H bond interactions between two molecules of the nucleophiles operating as an entity. The order in the dimer's stability is correlated with amine dimers that present H bonds involving oxygen atoms; this result allows explanation for the enhanced reactivity of arginine and dopamine, observed in the kinetic experiments. The experimental reactivity order was satisfactorily reproduced by the calculations in which the solvent was included.

Acknowledgements

Financial help from the Universidad Nacional del Comahue (grants no. I183 and I197-UNCo) and from Research and Development Institute of Process Engineering, Biotechnology and Alternatives Energies (PROBIEN) CONICET – Universidad Nacional del Comahue is gratefully acknowledged.

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