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ANS WITH METAL(II)-BIFUNCTIONAL AMINE COMPLEXES IN TOLUENE. KINETIC DETERMINATIONS AND QUANTUM CHEMICAL CALCULATIONS

SUSTITUCIÓN NUCLEOFÍLICA AROMÁTICA CON COMPLEJOS METAL(II)-AMINAS BIFUNCIONALES EN TOLUENO. DETERMINACIONES CINÉTICAS Y CÁLCULOS QUÍMICO CUÁNTICOS

Cecilia E. Silvana Alvaro[1,2*], Federico D. Bergero[3], Federico M. Bolcic[4], Susana B. Ramos[2,3], Norma S. Nudelman[5].

[1]Depto. de Química, Facultad de Ingeniería. Universidad Nacional del Comahue. Buenos Aires 1400 (8300) Neuquén, Argentina.
[2]Instituto de Investigaciones y Desarrollo en Ingeniería de Procesos, Biotecnología y Energías Alternativas (PROBIEN), CONICET - Universidad Nacional del Comahue, (8300) Neuquén, Argentina.
[3]Depto. de Física, Facultad de Ingeniería. Universidad Nacional del Comahue. Buenos Aires 1400, (8300) Neuquén, Argentina.
[4]Facultad de Ciencias Médicas, Universidad Nacional del Comahue. (8324) Cipolletti, Río Negro, Argentina.
[5]Academia Nacional de Ciencias Exactas, Físicas y Naturales, Avda. Alvear 1714, Piso 4, Buenos Aires, Argentina. Email: acad@ancefn.org.ar /sbarbati04@gmail.com

**Autor Corresponsal E-mail: silvanitaces@gmail.com / silvana_alvaro@hotmail.com*

Resumen

Se realizaron estudios cinéticos de Sustitución Nucleofílica Aromática (SNAr) empleando complejos Metal(II)-amina en tolueno y cálculos químicos cuánticos para determinar la geometría y energía de formación de los complejos. Los estudios previamente informados del mecanismo SNAr se centran principalmente en la naturaleza del sustrato, la basicidad del nucleófilo y la polaridad del disolvente, aunque el estudio con complejos de coordinación es escaso. Los complejos metal-amina exhiben una reactividad diferencial con respecto a las aminas no complejadas dependiendo, principalmente, del metal y la estructura del ligando. El presente trabajo describe estudios cinéticos realizados en tolueno con 1-cloro-2,4-

dinitrobenceno y complejos de Cu(II) y Fe(II) con aminas bifuncionales, y se compararon con estudios previos utilizando las aminas no complejadas. Considerando la diferente reactividad de los complejos metal-amina, los resultados sugieren una diferente labilidad de los complejos atribuidos al efecto quelato y efectos estereoelectrónicos, para formar aminas no complejadas que luego reaccionarían con el sustrato, ya que los resultados cinéticos no proporcionan evidencia que los complejos metal-amina reaccionan como entidad nucleofílica. Por el contrario, se disocian antes de reaccionar y los resultados obtenidos son consistentes con el mecanismo del "Nucleófilo Dímero". Mediante cálculos teóricos basados en la Teoría Funcional Densidad determinamos la estructura de equilibrio y energía de complejación de dichos complejos. Los cálculos teóricos indican que los complejos más estables son aquellos con tres moléculas de amina como ligando, y que los complejos de Cu(II) son más estables que los de Fe(II), resultados que se correlacionan con el orden de reactividad obtenido experimentalmente

Abstract

Kinetic studies of Aromatic Nucleophilic Substitutions (ANS) of Metal(II)-amine complexes in toluene and quantum chemical calculations were carried out. Reported studies of ANS mechanism are mainly centered on the nature of substrates, nucleophile basicity and solvent polarity, while the study with coordination complexes are scarce. Amine complexes exhibit a differential reactivity with respect to uncomplexed amines depending on, among other factors, the metal center and the ligand structure. The present work describes kinetic studies carried out in toluene with 1-chloro-2,4-dinitrobenzene (DNClB) and Cu(II) and Fe(II) complexes with bifunctional amines. They were chosen considering their characteristics of bi-dentate ligands, the possible size of the metalo-cycle formed and their ability to form intra- or intermolecular hydrogen-bonds. Taking into account the dissimilar reactivity of amine-complexes, the results suggest a different stability of the complexes attributed to stereo-electronic and chelate effects, to form uncomplexed amines that would then react with the substrate, since the observed results do not provide evidence that metal-amine complexes react as a nucleophilic entity. On the contrary, they seem to dissociate prior to react rendering results consistent with a “dimer nucleophile” mechanism. To interpret kinetic results, we performed Density Functional Theory calculations to determine the equilibrium structure and the binding energy for Cu(II) and Fe(II) amine complexes. Quantum chemical calculations indicate that the most stable complexes are those with three amines molecules as ligands, and that Cu(II) complexes are more stable than those with Fe(II), results that correlate with the order of reactivity experimentally obtained.

Palabras clave: Sustitución Nucleofílica Aromática; Solventes apróticos; Complejos de coordinación; Mecanismo del Nucleófilo Dímero; Cálculos DFT.

Keywords: Aromatic Nucleophilic Substitution; Aprotic solvents; Coordination complexes; Dimer Nucleophile Mechanism; DFT calculations.

1. Introduction

Transition metal complexes are currently receiving special attention due to their special biological activity (1,2), as well as for their applications in other scientific (3,4) and technological fields (5). Particularly, the investigation of structure and solvent effects on the reactivity of coordination metal complexes is an area of active interest (1-4). Studies on metal coordination complexes mainly refer to transmetalation, ligand substitution, displacement of ligand from a substrate M-L (where M is the metal and L is a ligand), or displacement of a leaving group from the ligand complex by various reagents (6). The amines form coordination complexes of particular significance in the development of Coordination Chemistry (7); particularly amine-transition metal complexes are very important chelates due to their biological implications. As some examples it can be mentioned the recently reported electro-reduction of mixed ligand cobalt (III) complexes (8), the metal chelation-assisted amine–amine electronic coupling through the 4,4′-positions of 2,2′-bipyridine (9), the metalloenzymes feature of the metals that are chelated, usually to peptides or cofactors and prosthetic groups[10], biological applications and nutritional supplements (11-14).

Studies of the Aromatic Nucleophilic Substitution (ANS) mechanism reported in the literature are mainly centered on the nature of substrates, nucleophile basicity and solvent polarity, while the coordination complexes study in ANS reactions are very scarce. The aim of the present work is to use metal amine coordination complexes as nucleophilic entities in ANS reactions, since they have the majority of their nucleophilic atoms forming coordinated covalent bonds with the metal, and therefore are expected to be mostly non-reactive. To examine the lability of such complexes and their possible capacity to dissociate in free amines that react with the substrate we synthesized metal amine coordination complexes, developed ANS reactions, characterized the ANS products obtained, and compared them with those obtained in our previous studies in which ANS reactions were performed with the same uncomplexed amines.

Early works were carried out on several ANS performed in aprotic solvents with nitro-activated substrates and poor leaving groups, for which the second-step of the reaction is rate-determining, providing kinetic, conformational and thermodynamical evidence for a new mechanism, called the "dimer nucleophile" for ANS with amines (15).

In the last years (16-19), we have reported ANS in aprotic solvents with a substrate having a good leaving group and amines that were purposefully selected due to their special structure that make them able to form inter- or intramolecular H-bonds, as were determined by NMR measurements (20). Theoretical calculations were also performed on these amines to provide valuable insight into the predominant type of H-bonds present in them (21,22). Due to the self-aggregation and other non-covalent interactions that occur in solvents of low permittivity, the predominant nucleophile is the dimer of the amine. In these cases, a third order in amine concentration, giving an overall fourth-order kinetics was determined. These reactions occur via an addition/elimination mechanism where the first step is the attack of the amine dimer to the substrate (k_1) to form a zwitterionic σ-bonded complex (SB), usually named Meisenheimer complex. In a second step, the leaving group detaches from the substrate to give the reaction product. This step can be uncatalyzed (k_2), or occur through a catalyzed route (k_3) by a third nucleophilic molecule as it has been reported in previous works (15-17).

The present paper describes ANS reactions developed with metal complexes of amines. Specifically, these reactions were carried out with 1-chloro-2,4-dinitrobenzene, (DNClB), a good nucleofugue substrate, and several coordination complexes of bifunctional amines with Cu(II) and Fe(II), in toluene. The amines are ethylenediamine (EDA), N,N-dimethyl propylamine (DMPA), 2-(1H-imidazol-4-yl)ethanamine, (histamine), and 1-(2-aminoethyl)piperidine, (2-AEPip). They were selected by considering their characteristics of bi-dentate ligands and the possible size of the metalo-cycle formed. As a way of comparison, we have previously studied ANS with the uncomplexed amines (18).

In order to provide theoretical insights on the interpretation of the kinetic results, Density Functional Theory (DFT) (23) calculations on Cu(II) and Fe(II) complexes with the above mentioned amines were carried out, determining the optimal geometries in vacuum and their binding energies. Theoretical studies based on DFT methods currently provide information about the strength, ionic character of bonds, the charge transfer effects (24-26). Analysis based on the Atoms in Molecules (27) theory were also carried out to characterize the relevant covalent bonds and also the weak interactions present in the coordination complexes used in the study.

2. Materials and Methods

2.1. General Procedures

UV-VIS spectra and kinetic runs were recorded in a Shimadzu UV-VIS 240 graphic printer PR-1 spectrophotometer. 1H and 13C NMR spectra were recorded in a Bruker ARX-300 spectrometer instrument. NMR spectra were determined in CDCl3 spectroscopic grade as solvent and the J values are given in hertz. The infrared spectra were recorded on a Nicolet spectrophotometer, Nexus FT-IR 470/670/870. Thin-layer chromatography was performed on Merck Kiesegel 60 F254. Melting points were determined in a Kofler hot stage and are uncorrected.

2.2. Reagents and Solvents

The reagents and solvent used are the commercially available from Merck, Fluka and Sigma-Aldrich which guarantee purity ≥ 99%. Toluene was kept over sodium wire for several days and distilled twice over sodium as described previously (16). The purification of EDA, DMPA and 2-AEPip were carry out as described previously (18) and kept in a desiccator protected from light under dry nitrogen atmosphere, prior to use. 2-(1H-imidazol-4-yl)ethanamine, (Fluka) was used without any purification and was kept in a desiccator protected from light.The substitution products were purified and characterized by NMR spectra using previously reported procedures (18).

The complexes were prepared as reported elsewhere (28), using an ethanolic solution of iron(II) and copper(II) ammonium sulfate and the respective amine. The Fe(II) complexes were prepared in the presence of drops of glacial acetic acid to avoid Fe(II) oxidation. The formation of the amine-Cu(II) complexes was shown by the appearance of a blue coloration in the colorless amine solutions after the addition of the metal ion solution; the spectra of the solutions of each ligand were performed in the absence and by adding the solution of the metal ion to the solution of the ligand in toluene and were recorded between 250 and 650 nm. After the addition of the Cu(II) solution new bands among 540-580 nm can be attributed to the amine-Cu(II) complexes formation, considering that neither the metallic ion nor the ligands absorbs in that wavelength range. A similar procedure was used for the amine-Fe(II) complexes, a green color solution was observed when adding the Fe(II) salt. Two bands, centered on 430-455 and 600-610 nm were observed in the spectra and can be attributed to the amine-Fe(II) complexes formation.

Stoichiometries of the formed complexes were determined using the Yoe-Jones method (29). This spectrophotometric method requires the preparation of a set of solutions varying the ligand concentration [L], but keeping constant the metallic ion concentration [M]. The absorbance, A, of these solutions was measured at a wavelength which only the complexes absorb, and used to plot a graphic of A vs. [L]/[M]. The intersection points between the straight lines of the experimental data indicate the ligand:metal L:M molar ratio. It was found that the stoichiometries of the formed complexes were 3:1 ligand:metal molar composition.

The spectroscopic characterization of the substitution products was made by IR and NMR spectroscopic determinations and coincided with those obtained in the previous study where these reactions were studied with the same substrate and solvent using the uncomplexed amines (18). The characterization results are presented below:

[N-(2,4-dinitrophenyl)ethylenediamine] (mp 108-110 °C), 1H NMR ($CDCl_3$): δ 2.30 (s, ^1H), 8.93 (d, ^1H), 6.87 (d, 1H), 8.12 (m, 1H), 3.28 (t, 2H), 3.00 (t, ^2H), 1, 40 (s, 2H), ^{13}C NMR ($CDCl_3$): δ

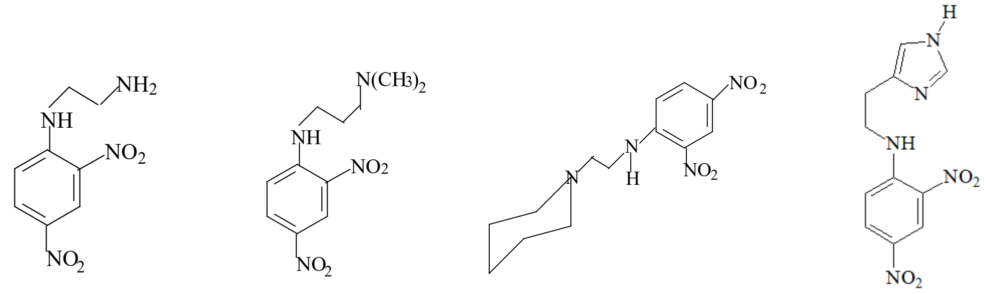
40.90, 48.31, 121.51, 121.87, 132.55, 148.10, 148.50, 149.90]. IR (KBr) ν cm^{-1}: 3320 (-N-H); 2850 (C-H, -CH_2); 1640 (-NH_2); 1590 (C-C); 1510 (-NO_2); 1470 (C-H -CH_2); 1340 (-NO_2); 1120 (-C-N); 890 (C-H); 780 (two bands, -NH_2); 710 (C-H)].

[3-dimethylamino-1-N-(2,4-dinitrophenyl)propylamine] (mp 100-102 ºC), ^{1}H NMR ($CDCl_3$): δ 2.10 (s, 1H), 9.30 (d, 1H), 7.40 (d, 1H), 8.48 (m, 1H), 3.70 (t, 2H), 2.01(t, 2H), 2.65 (t, 2H), 2.31 (s, 6H), ^{13}C NMR ($CDCl_3$): δ 27.65, 44.48, 45.40, 58.01, 119.34, 122.35, 128.87, 147.80, 148.48, 149.90]. IR (KBr) cm^{-1}: 3320 (N-H); 2850 (C-H, -CH_2); 1658 (-N-H); 1500 (-NO_2); 1470 (-C-H, -CH_2); 1340 (-NO_2); 1380 (C-H, -CH_3); 1120 (C-N); 860 (-C-H); 740 (C-H).

[N-(2,4-dinitrophenyl)-1-(2-aminoethyl)piperidine] (mp 122-123 ºC), ^{1}H NMR ($CDCl_3$): δ 9.04 (s, 1H), 8.15 (d, 1H), 6.81 (d, 1H), 3.36 (t, 2H), 2.63 (t, 2H), 2.40 (t, 4H), 1.49 (m, 6H), 1.02 (s, 1H). ^{13}C RMN ($CDCl_3$) δ 150.91, 148.50, 147.15, 131.52, 120.77, 115.34, 49.70, 47.90, 43.80, 27.80, 25.90. IR (KBr) ν cm^{-1}: 3480 (N-H), 1530 (N-H), 1540 and 1380, (-NO_2)].

[N-(2,4-dinitrophenyl)histamine] (mp 158-160 °C), ^{1}H NMR ($CDCl_3$): δ 12.60 (s, 1H), 9.03 (s, 1H), 8.25 (d, 1H, 3JHH = 9.5 Hz), 8.08 (s, 1H), 7.59 (s, 1H), 7.10 (d, 1H, 3JHH = 9.5 Hz), 3.20 (t, 2H), 3.05 (t, 2H), 2.30 (s, 1H), ^{13}C NMR (CDCl3) ppm: δ 150.91, 148.50, 147.15 , 136.20, 131.52, 122.40, 121.30, 120.77, 115.34, 38.79, 23.19. IR (KBr) ν cm^{-1}: 3450 (N-H); 2750 (C-H, -CH_2); 1640 (N-H); 1590 (C-C); 1510 (C-C); 1500 (-NO_2); 1455 (C-H, -CH_2); 1340 (-NO_2); 880 (C-H); 770 (δ C-H).

The structures of the substitution products are shown in Figure 1.



1 2 3 4

Figure 1. Molecular structures of the ANS products from 1) ethylenediamine, 2) N, N-dimethylpropylamine, 3) 1-(2-aminoethyl)piperidine, 4) histamine.

2.3. Kinetic Procedures

Kinetic measurements of ANS reactions were performed under pseudo first-order conditions by the methods previously reported at the maximum wavelength of each substitution producto (18) as follows: [2-Amino-1-N-(2,4-dinitrophenyl) ethylamine: λ_{max} = 348 nm; [4(5)-2'-(N-2,4-dinitrophenyl) aminoethyl imidazole: λ_{max} = 349 nm; [3-dimethy1amino-1-N-(2,4-dinitropheny1) propylamine: λ_{max} = 351 nm; [N-(2,4-dinitrophenyl)-1-(2-aminoethyl) piperidine: λ_{max} = 348 nm, at 25 ± 0.2 °C.

The reactions of histamine-metal complex were carried out in sealed ampoules (under nitrogen) and the reactions of EDA, DMPA and 2-AEPip complexes were followed directly in the thermostatic cell of the spectrophotometer at 25 ± 0.2 ºC. The zero-time concentration of metal-amine complexes was between 0.4 – 1.20 M, and were prepared in solution immediately before being used. At those wavelengths the reagents are transparent under the experimental conditions.

Pseudo-first-order coefficients, k_Ψ, were obtained by the least-squares method as the slope of the correlation ln $(A_\infty - A_t)/A_\infty$ versus time, where A_∞ is the optical density of the reaction mixture measured at infinite time (more than ten half-lives). The absorption spectrum of the reaction mixture at "infinite time" corresponded within ± 4 % with the "theoretical" value calculated by application of Beer's law to solutions of the product independently prepared in toluene. No corrections for expansion coefficients were applied to the concentration values.

2.4. Computational procedures

We considered complexes formed with Cu(II) and Fe(II) and one to three ligands of the amines EDA, DMPA, histamine and 2-(AEPip).

First of all, a relaxed Monte-Carlo automatic exploration of the potential energy surface was carried out using the PM6 (30) semiempirical model for the geometrical optimizations. Out of the resulting conformations, the highest energies were discarded according to an energy criterion based on the Boltzmann distribution, usually .003 to .005 au above the lowest energy conformer. Of them, only those significantly different (i.e., different bonding pattern) were chosen, usually one to three. These semiempirical conformer searches have been recommended and the conformer energies have been found to have good correlation with the DFT ones (31).

Then, the selected conformers were optimized by the spin-unrestricted DFT (23) method and the B3LYP (24) exchange-correlation potential using the Gaussian 09 program (32). For Fe and Cu atoms, the LANL2DZ basis set and effective core potential (ECP) were used, and for the lighter atoms, the 6-31+G(d) basis set. In some cases, namely complexes of EDA and DMPA of one to three ligands, several spin multiplicities were tested by the unrestricted PM6 and/or the mentioned unrestricted DFT method. The multiplicities tested were mainly one and five, in the smallest complexes, also three and seven for Fe(II), and mainly two and four for Cu(II) complexes. It was found that complexes with multiplicity five for Fe(II) and two for Cu(II) have the minimal energy. Although in the case of Fe(II) this contradicts previous calculations done on porphyrines, in which the B3LYP functional favors multiplicities three or one (33a), this is consistent with experimental data referenced therein. So, all further calculations and results reported here were carried out for those spin multiplicities.

As a final step, the energies of one or two lowest energy conformers were recalculated using the LANL2TZ(f) (34) basis set and ECP for Fe and Cu atoms, and the 6-311+g (2d, p) basis set for the lighter atoms. That step included basis set superposition error (BSSE) correction using the Counterpoise (CP) method (35). Out of those, the minimum energy conformers for each species are those presented here and discussed in the result´s section.

Amine monomers and dimers were also calculated by the same procedures and models, as their energies are used for calculating several results. Monomers do not require CP corrections. Metal atoms were also calculated with the same models. They require no geometrical optimization or CP correction.

All energies were calculated in vacuum at 0 K. In CP and in monomer and ions calculations, all unbalanced charges and unpaired electrons were assumed to be in the metal ion.

Complexes with four ligands were also searched by the same Monte Carlo semiempirical method as the other complexes. No further DFT calculations were carried out on them because in most cases the 3:1 complexes were found to be energetically more stable at the PM6 level, and also because the Yoe-Jones (29) experimental results favor the 3:1 ones (see sections 2.2 and 3).

The reported binding energy Eb of the complexes is the CP-corrected “complexation energy” as given by the G09 software (32). It is defined as the counterpoise-corrected total energy of the complex minus the energies of each fragment calculated separately with the same geometry it has within the complex. So, it measures the binding interaction of all the parts within the complex.

We also report E_b divided by the number of ligands N_l (E_b/N_l) and by the number of N-metal coordinated covalent bonds N_b (E_b/N_b). The former is roughly the energy required to remove one amine from the complex or its tendency to provide an amine for the ANS reaction. So, it is an estimation of the lability and reactivity of the complex. The latter is roughly related to the bond strength of the N-metal coordinated covalent bonds, although amine-amine interactions are also part of that number.

The reported complex formation energy ΔE_{form} is defined as the complex's CP corrected energy minus the energies of the isolated (and geometry optimized) ligands and metal ions, thus including the geometry effect. It is related to the relative abundance of different possible complexes that form in the solvent. Those with greater (more negative) ΔE_{form} are more abundant.

The energies ΔE_1, ΔE_2 and ΔE_3 are the energy differentials when dissociating the complexes. For example, for 3:1 complexes, ΔE_1 corresponds to removing one amine from the complex, leaving a 2:1 complex and a free amine, all with their relaxed geometries. ΔE_2 would correspond to removing two amines from it, leaving a 1:1 complex and two free amines, all geometrically relaxed. ΔE_3 would be further dissociating the remaining 1:1 complex, so it is exactly the opposite of ΔE_{form}. Likewise, ΔE_1 and ΔE_2 are equal in absolute value to the ΔE_{form} of a 1:1 and a 2:1 complex respectively.

For amine dimers, E_b is the binding energy, defined and calculated the same as for metal-amine complexes.

The presence of hydrogen bonds as well as coordinated covalent bonds was verified according to the AIM theory (27) with the multiWFN software (36). 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 (36). The positive sign of the Laplacian found in all H-bonds also shows their closed-shell (non-covalent) nature (27). The ellipticity ε at the BCP shows the electron density's deviation from circular symmetry: $\varepsilon = 0$ indicates a perfectly symmetric bond, i.e., 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 (27).

All atomic charges were also calculated according to the AIM theory. A space region called atomic basin is defined as the region bounded by closed surfaces through which the flux of the gradient vector field of the electron density is zero. The number of electrons n_e contained in the atomic basin is the integral of ρ in its volume, and the atomic charge is therefore -(ne-Z) (27). For the metal-amine complexes, we also calculated the atomic charges of the amines alone, with the same geometry that they have in the complex. So we define a charge transfer number Δq for each atom as $q_{complex} - q_{alone}$, i.e., the charge change due to the interaction with the metal atom and the other amines in the complex. This number is indicative of the intermolecular interactions in which each atom participates in the complex (25, 26).

3. Results and Discussion

3.1. *Kinetic results*

There is at present a considerable interest in the experimental and theoretical research of transition metal coordination complexes concerning their structures and stability (2, 8-10).

One of the first reports on the subject was informed by Shehata *et al.*(6) who proposed an ANS-like mechanism with [1-arylethanediylidene-bis-(methyldithiocarbazonoate)NN'SS'(−2)]Ni(II) complexes and morpholine in benzene in which the rate-determining step is the proton transfer process in the temperature range 20–35 ºC. The mechanism in the range 40–55 ˚C proceeds through the attack of morpholine on the carbon carrying a SCH_3 group followed by the addition of the second morpholine molecule on Ni to form an intermediate, which undergoes the elimination of morpholine and CH_3SH to give a monosubstituted complex.

The present paper reports determinations of the reactivity of Cu(II) and Fe(II)-amine complexes in ANS carry out in an aprotic solvent. The selected amines were chosen considering their characteristics of bi-dentate ligands and for the potential influence on the size of the metalo-cycle formed.

Reactions of DNClB with Cu(II) and Fe(II) amine complexes in toluene

The kinetics of the reactions between DNClB and Cu(II) and Fe(II) EDA, DMPA, 2-AEPip and histamine-metal complexes, respectively, carried out in toluene, were studied at 25 ± 0.2 ºC in the presence of variable amounts of amine complexes. The reactions proceed straightforwardly to give the expected N-substituted 2,4-dinitroaniline, shown in Figure 1.

The kinetic constants are compared with previous kinetic results obtained with the uncomplexed amines. Tables 1 and 2 shows the bimolecular rate coefficients, k_A, and third order rate coefficients, k_A/[B], for the uncomplexed amines and metal-amine complex reactions under the same reaction conditions.

Table 1: Reaction of 2,4-dinitrochlororobenzene, DNClB, with 1,2-diaminoethane (EDA), and 3-dimethylamino-1-propylamine (DMPA), and their respective complexes with Cu(II) and Fe(II) in toluene at 25.0 ± 0.2ºC. Second- (k_A), and third- (k_A/[B]) order rate coefficients are indicated.

[EDA][a*], M	0.494	0.60	0.704	0.794	0.899	1.00	1.20	1.50	----
10^3k_A, s^{-1} M^{-1}	1.69	2.25	2.84	4.11	4.52	6.21	8.39	13.50	----
10^3k_A/[B], s^{-1} M^{-2}	3.42	3.75	4.03	5.18	5.03	6.21	6.99	8.98	----
[Fe(II)-EDA][b], M	0.40	0.60	0.70	0.80	0.90	1.00	1.20	----	----
10^4k_A, s^{-1} M^{-1}	0.54	1.03	1.25	1.60	2.01	2.37	3.15	----	----
10^4k_A/[B], s^{-1} M^{-2}	1.35	1.72	1.79	2.00	2.24	2.37	2.63	----	----
Cu(II)-[EDA][b], M	0.40	0.60	0.70	0.80	0.90	1.00	1.20	----	----
10^5k_A, s^{-1} M^{-1}	0.42	0.65	0.79	0.86	1.11	1.35	1.85	----	----
10^5k_A/[B], s^{-1} M^{-2}	1.05	1.08	1.13	1.08	1.23	1.35	1.54	----	----
[DMPA][a*], M	0.497	0.601	0.697	0.800	0.897	1.00	1.20	1.50	2.01
10^3k_A, s^{-1} M^{-1}	0.480	0.72	0.99	1.26	1.55	1.98	2.59	3.93	5.92
10^3k_A/[B], s^{-1} M^{-2}	0.976	1.20	1.42	1.57	1.73	1.98	2.16	2.62	2.94
[Fe(II)-DMPA][b], M	0.40	0.60	0.70	0.80	0.90	1.00	1.20	----	----
10^4k_A, s^{-1} M^{-1}	0.45	0.96	1.21	1.93	2.40	2.75	3.93	----	----
10^4k_A/[B], s^{-1} M^{-2}	1.12	1.60	1.73	2.41	2.67	2.75	3.27	----	----
Cu(II)-[DMPA][b],M	0.40	0.60	0.70	0.80	0.90	1.00	1.20	----	----
10^5k_A, s^{-1} M^{-1}	0.33	0.56	0.72	1.03	1.29	1.49	1.98	----	----
10^5k_A/[B], s^{-1} M^{-2}	0.82	0.93	1.03	1.29	1.43	1.49	1.65	----	----

[a][DNClB] = 5.0 x 10^{-4}M. [b][DNClB] = 5.1 x 10^{-4} M.
*data taken from reference 18.

Table 2: Reaction of 2,4-dinitrochlororobenzene, DNClB, with 1-(2-aminoethyl)-piperidine, 2-AEPip and histamine (His) and their respective complexes with Cu(II) and Fe(II) in toluene at 25.0 ± 0.2ºC. Second- (k_A), and third- (k_A/[B]) order rate coefficients are indicated.

[2-AEPip][a*], M	0.496	0.597	0.79	0.99	1.20	1.51	1.73	2.01
10^3k_A, s^{-1} M^{-1}	1.92	2.48	3.12	4.88	5.98	8.73	10.09	15.40
10^3k_A/[B], s^{-1} M^{-2}	3.87	4.15	3.95	4.88	4.98	5.78	6.30	7.66
[Fe(II)-2-AEPip][b], M	0.40	0.60	0.70	0.80	0.90	1.00	1.20	----
10^4k_A, s^{-1} M^{-1}	0.65	1.12	1.35	1.73	2.19	2.49	3.35	----
10^4k_A/[B], s^{-1} M^{-2}	1.62	1.86	1.93	2.16	2.43	2.49	2.79	----
[Cu(II)-2-AEPip][b], M	0.40	0.60	0.70	0.80	0.90	1.00	1.20	----
10^5k_A, s^{-1} M^{-1}	0.45	0.63	0.80	0.96	1.16	1.40	1.62	----
10^5k_A/[B], s^{-1} M^{-2}	1.12	1.05	1.14	1.20	1.29	1.40	1.35	----
[His]*, M	0.25	0.50	0.70	0.90	1.20	1.50	1.85	2.10
10^5k_A, s^{-1} M^{-1}	1.20	3.90	5.60	7.20	9.30	10.6	12.8	15.0
[Fe(II)-His][b], M	0.40	0.60	0.70	0.80	0.90	1.00	1.20	----
10^6k_A, s^{-1} M^{-1}	0.97	1.47	1.75	2.10	2.55	2.81	3.50	----
[Cu(II)-His][b], M	0.40	0.60	0.70	0.80	0.90	1.00	1.20	----
10^7k_A, s^{-1} M^{-1}	0.30	0.51	0.65	0,78	0.93	1.02	1.27	----

[a][DNClB] = 5.09 x 10^{-4}M. [b][DNClB] = 5.12 x 10^{-4}M.
*data taken from reference 18.

Assuming that the complexes are at least partially dissociated in solution, diverse species may be present in the reaction media. However, considering the different binding energy (E_b) per bond and per ligand calculated theoretically (Table 3), it can be inferred that the species present in solution that react with the substrate are the uncomplexed amines, which can undergo self-association forming dimers, taking into account that self-aggregation of the amines prevails in non-polar aprotic solvents (15), and that the metal amine complexes partially dissociated, formed with two or three amine molecules are non-nucleophilic entities (see below Scheme 1, eq. 1). As shown in Figures 2-4, the second-order rate coefficients k_A of the reactions of metal-EDA, 2-AEPip and DMPA complexes with DNClB in toluene show a quadratic dependence with the amine complex concentrations.

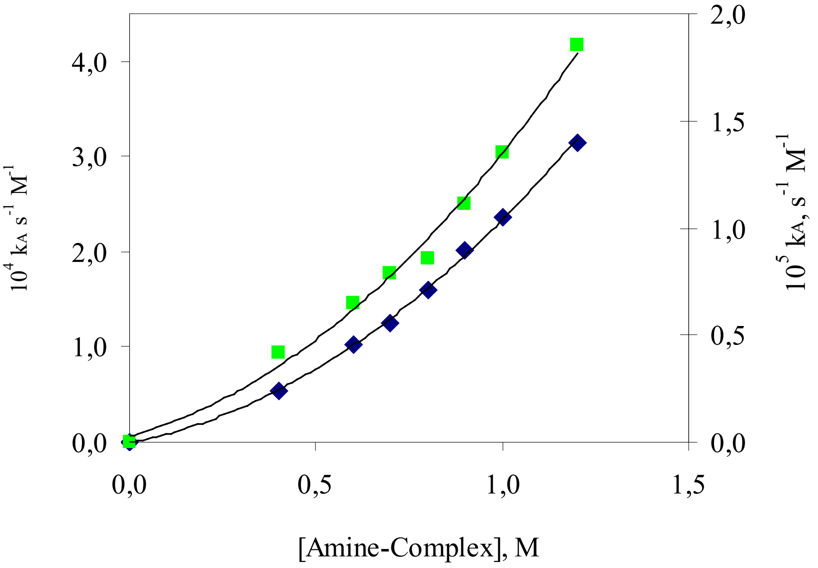


Figure 2: Second-order rate coefficients, k_A, for the reactions of 2,4- dinitrochlorobenzene (DNClB) with ■ EDA- Cu(II) complex (105 right Y-axis scale), and • EDA-Fe(II) (104 left Y-axis scale), in toluene at 25.0 ± 0.2 ºC, respectively, as a function of [amine-complex].

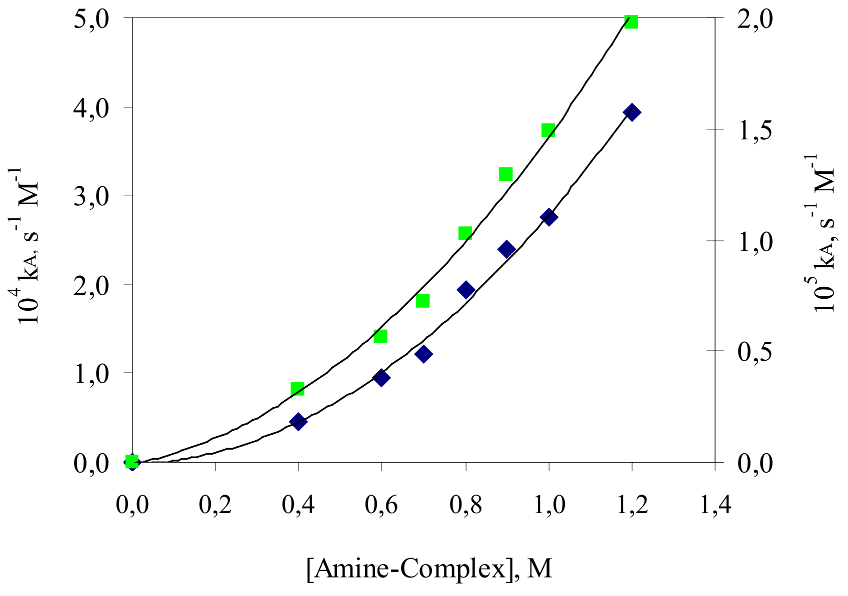


Figure 3: Second-order rate coefficients, k_A, for the reactions of 2,4- dinitrochlorobenzene (DNClB) with ♦ DMPA-Fe(II) (10^4 left Y-axis scale) and 🟩 DMPA-Cu(II) (10^5 right Y-axis scale) in toluene at 25.0 ± 0.2 ºC, respectively, as a function of [amine-complex].

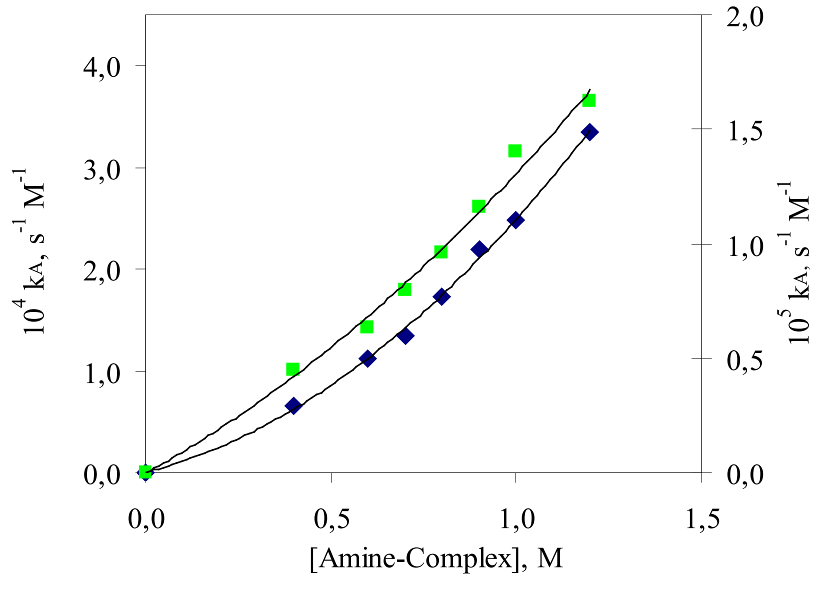


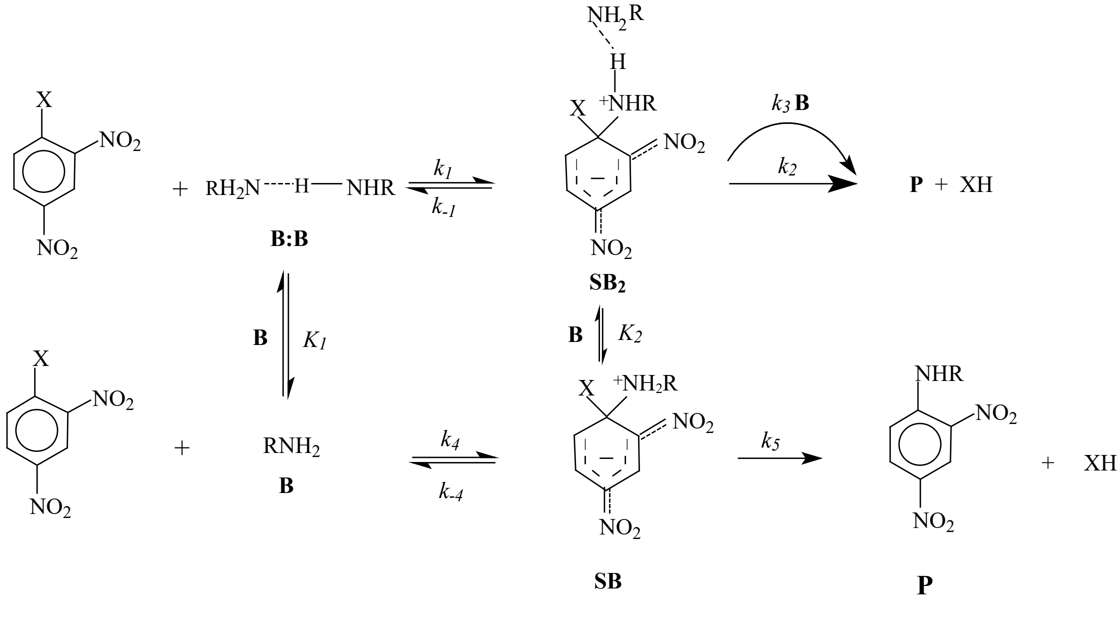
Figure 4: Second-order rate coefficients, k_A, for the reactions of 2,4- dinitrochlorobenzene (DNClB) with ■ 2-AEPip-Cu(II) (105 right Y-axis scale) and • 2-AEPip-Fe(II) (104 left Y-axis scale) in toluene at 25.0 🟩 0.2 ºC, respectively, as a function of [amine-complex].

For complexes formed with EDA, DMPA and 2-AEPip, at low concentration of metal-amine complexes, the kinetic behavior seems to be linear, however at higher concentrations an upward curvature is observed. In these Figures, different scales for the k_{A} values are used due to their different reactivity. Also, the third-order rate coefficients for these reactions show a straight line (data not shown). These results are consistent with a third-order in the amine term in the kinetic law at high concentration complexes.

Regarding the self-aggregation and other non-covalent interactions that occur in solvents of low permittivity, the kinetic data shown in Figures 2-4 indicate that the predominant nucleophile is the dimer of the amine, and in these cases, a third order in amine concentration is obtained, giving an overall fourth-order kinetics. Application of the steady-state treatment to the whole mechanism gives an expression involving specific rate constant for each step and the association equilibrium constant for the nucleophile, K. Derivation of the complete expression and the limit situations that were evaluated are described in ref. 19. The simplified reaction scheme which includes the dissociation of the metal-amine complexes studied in this work, is shown in Scheme 1. The proposed mechanism does not preclude attack by the monomer, as shown in the step pathway depicted below:

$$(\text{Metal} — 3\text{NH}_2 — \text{R})_{\text{complex}} \overset{K_{dis}}{\rightleftarrows} (\text{Metal} — 2\ \text{NH}_2 — \text{R})_{\text{complex}} + \text{NH}_2 — \text{R} \qquad (1)$$

$$2\ \text{RNH}_2 \rightleftarrows \text{RNH}_2 \cdots \text{NH}_2\text{R} \qquad (2)$$



(3)

$$k_A = \frac{k_1 k_2 K[B] + k_1 k_3 K[B]^2}{k_{-1} + k_2 + k_3[B]} \qquad (4)$$

Scheme 1: Reaction for metal-amine complexes and EWG substrate of Dimer Nucleophile Mechanism by amine dimer and monomer amines and the corresponding kinetic expression for the reaction.

Eq. 1 of Scheme 1 represents the first dissociation equilibrium reaction of a amine-metal complex formed with three amine molecules, which liberates one amine molecule. Eq. 2 represents the auto-association of the free amines that exists in solution, through H-bonding. While the complex with two amine molecules could further dissociate, the first dissociation of a single amine molecule appears to be the most likely, according to the calculated binding energies (E_b/N) of each ligand in the complex (see Table 3).

By the contrary, a linear dependency is observed in the case of histamine.

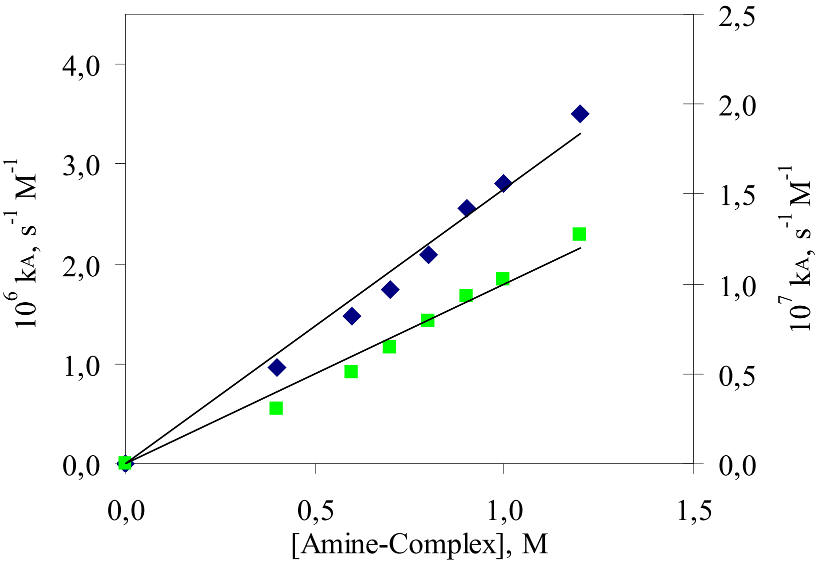
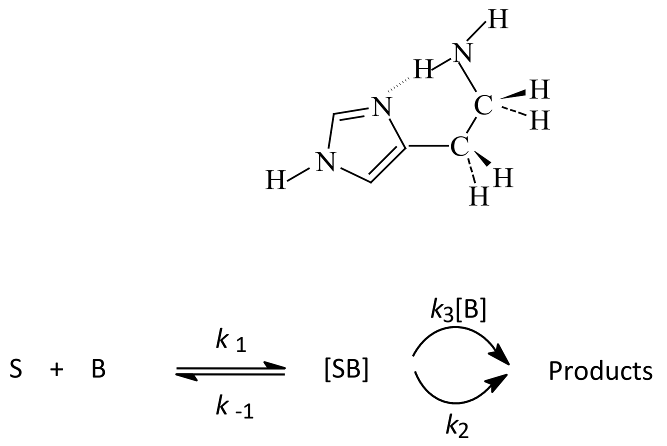


Figure 5: Second-order rate coefficients, k_A, for the reactions of 2,4- dinitrochlorobenzene (DNClB) with ■ histamine-Cu(II) (10^7 right Y-axis scale) and ♦ histamine-Fe(II) (10^6 left Y-axis scale) in toluene at 25.0 ± 0.2ºC as a function of [amine-complex].

Figure 5 shows the kinetic behavior of histamine-metal(II) complexes with DNClB in toluene, in presence of variable amounts of the nucleophile. The second-order rate coefficients increase steadily with [histamine-complex] (eq. 5); the plot of k_A vs. nucleophile is a straight line with a null intercept and a correlation coefficient of R2 = 0.984 for histamine-Fe(II) complex and $R^2 = 0.977$ for Cu(II). In histamine, an intramolecular hydrogen bond prevents the formation of intermolecular dimers (Scheme 2) and the classical mechanism of base-catalyzed decomposition of SB (eq. 5) is obeyed (18). The null intercept indicates that the spontaneous decomposition of SB is negligible. The proposed histamine structure that should act as a nucleophile is shown below, where a six-membered ring is formed by an intramolecular hydrogen bond:



(5)

Scheme 2: Intramolecular hydrogen bond established in histamine in aprotic solvents and the reaction scheme.

Considering the self-aggregation of amines in aprotic solvents and the different reaction rates obtained with the different metal-amine complexes, these results suggest distinct stabilities for each complex, attributed to stereo-electronic and chelate effects. Differences in the stability of the complexes, can also be presumed from the theoretical results (see below).

Therefore, the different stability of the metal-amine complexes appears as the main determinant factor controlling the nucleophilic attack process in these ANS reactions. The observed kinetic results do not provide evidence that the metal-amine complexes react as a nucleophilic entity. On the contrary, they seem to dissociate prior to react rendering results consistent with a "dimer nucleophile" mechanism for ANS. The structures of these amines may allow the formation of intra- or intermolecular H-bond in the complex structure influencing its stabilization energy, serving as an indicator of the gradual change of strength and reactivity of many types of complexes (37).

In the present study, the reaction rates of the complexes are one and two orders of magnitude lower with respect to uncomplexed amines (18). Reactions with Cu(II) complexes are slower than those obtained with Fe(II) complexes, consistently with the relative stabilities (see Tables 1 and 2). In summary, the reactivity trends are controlled by the lability of the different complexes, as has been recently reported (38).

3.2. Theoretical results

Figure 6 (a) to (h) shows the most stable complexes (greater negative ΔE_{form}) of EDA, DMPA, histamine and 2-AEPip with Fe(II) and Cu(II). All of them are those with a coordination number of three. The coordinated covalent bonds and H-bonds found by the AIM method are shown in dashed lines.

In both EDA-Fe(II) and histamine-Fe (II), six N atoms form coordinated bonds to the Fe ion, leading to an approximately symmetrical tetragonal geometry. For EDA-Fe(II), the N-Fe-N dihedral angles for the same ligand are ≈ 75º and in histamine-Fe, ≈ 88º.

In all 3:1 amine-Cu(II) complexes and in 2-AEPip-Fe(II) and DMPA-Fe(II) 3:1 complexes, only five N atoms form coordinated bonds with the metal ions, and the remaining one forms a hydrogen bond. This could be due to steric effects preventing all molecules from fully approaching the metal ion and to the stabilization effect of the H-bond.

In EDA-Cu(II) the geometry is nearly square pyramidal, with both dihedral and out-of-plane angles ≈ 99º maximum. So it is in histamine-Cu(II), with dihedrals of ≈ 88º and out-of planes of ≈ 104º maximum, and in 2-AEPip-Cu(II), with dihedrals of ≈ 83º to ≈ 96º and an out-of plane of ≈ 105º maximum. In DMPA-Cu(II), the geometry is trigonal bipyramidal, with dihedral angles ≈ 109º to 127º for the base of the pyramid and out-of planes angles of ≈ 83º minimum. DMPA-Fe(II) has the same geometry, with dihedral angles of ≈ 112º to 129º and out-of plane angles of ≈ 84º minimum. So does 2-AEPip Fe(II), with dihedrals of ≈ 108º to 137º and out-of-planes of ≈ 79º minimum.

The coordination numbers and geometries found are consistent with previous studies on Cu(II) (33b) and Fe(II) (33a) complexes, which also found five or six bonds, four of them planar and the other or others on a perpendicular axis.

In all cases of the intra- or intermolecular H bonds formed, the proton donor is a primary nitrogen which is also engaged in a coordinated bond to the metal atom. In both DMPA complexes, H bonds are intramolecular and the acceptor is a tertiary nitrogen. The same H-bonding pattern was found in a previous study of the uncomplexed amines (22). 2-AEPip-Fe(II) has an intramolecular H-bond between a primary and a tertiary nitrogen, which was not seen in the mentioned study. In the remaining complexes, H-bonds are intermolecular, and in 2-AEPip-Cu(II), the proton acceptor is a tertiary N, while in EDA-Cu(II) and histamine-Cu(II), it is a primary N.

Table 3 shows characteristics of complexes of Fe(II) and Cu(II) with EDA, DMPA, histamine and 2-AEPip, with a number of amine ligands (N_l) of one to three. These characteristics are: the total number of coordinated covalent bonds (N_b) between amine N atoms and the metal atom, (as shown in Figure 5), the binding energy (E_b), the binding energy per N-metal bond (E_b/N_b), the binding energy per ligand (E_b/N_l), and the complex formation energy (ΔE_{form}), all calculated as described in the Computational Procedure section.

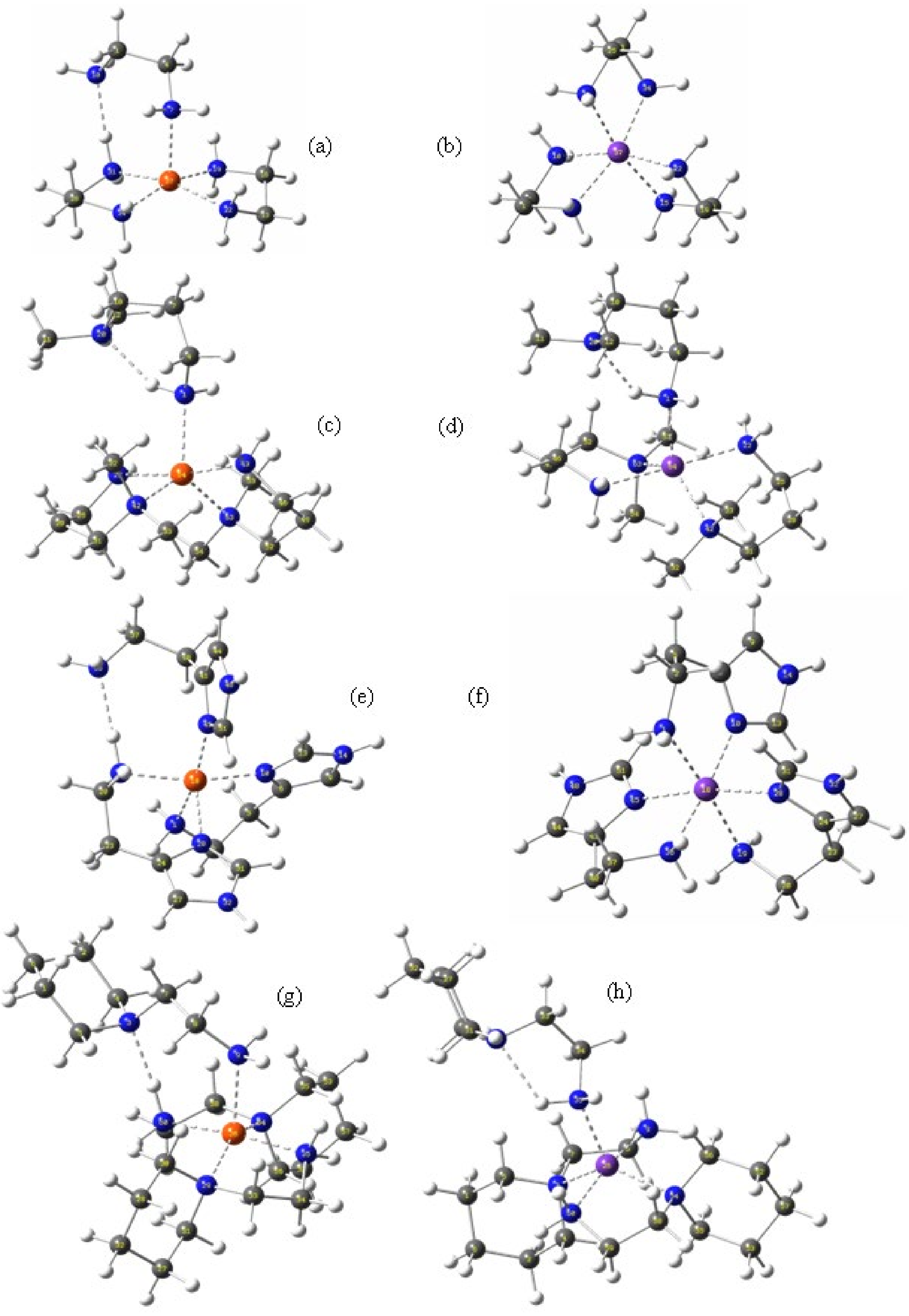


Figure 6: Calculated structure and bonding of 3:1 amine-metal complexes. (a) EDA-Cu(II); (b) EDA-Fe(II); (c) DMPA-Cu(II); (d) DMPA-Fe(II); (e) Histamine-Cu(II); (f) Histamine-Fe(II); (g) 2-AEPip-Cu(II); (h) 2-AEPip-Fe(II).

Note: Grey: C; white: H; blue: N; purple: Fe; red: Cu. Dashed line: H-bond or coordinated bond.

Table 3: Number of amine ligands, number of N-metal bonds, formation and binding energies (kcal/mol), for complexes of Cu(II) and Fe(II) with 1 to 3 EDA, DMPA, histamine and 2-AEPip ligands. See abbreviations in the text.

Amine-Fe(II)									
	N_l	N_b	E_b	E_b/N_b	E_b/N_l	ΔE_1	ΔE_2	ΔE_3	ΔE_{form}
EDA	**1**	2	-207.8	-103.9	-207.8	199.8			-199.8
	2	4	-328.4	-82.1	-164.2	114.4	314.2		-314.2
	3	6	-379.1	-63.2	-126.4	46.9	161.3	361.1	-361.1
DMPA	**1**	2	-237.2	-118.6	-237.2	227.7			-227.7
	2	4	-339.9	-85.0	-170.0	92.4	320.2		-320.2
	3	5	-382.8	-76.6	-127.6	38.0	130.4	358.1	-358.1
Histamine	**1**	2	-249.6	-124.8	-249.6	238.7			-238.7
	2	4	-372.3	-93.1	-186.2	117.1	355.7		-355.7
	3	6	-415.1	-69.2	-138.4	37.6	154.6	393.3	-393.3
2-AEPip	**1**	2	-237.7	-118.9	-237.7	226.6			-226.6
	2	4	-345.6	-86.4	-172.8	95.8	322.5		-322.5
	3	5	-380.1	-76.0	-126.7	31.4	127.2	353.9	-353.9

Amine-Cu(II)									
	N_l	N_b	E_b	E_b/N_b	E_b/N_l	ΔE_1	ΔE_2	ΔE_3	ΔE_{form}
EDA	**1**	2	-266.4	-133.2	-266.4	257.1			-257.1
	2	4	-393.3	-98.3	-196.6	120.5	377.6		-377.6
	3	5	-429.0	-85.8	-143.0	30.2	150.7	407.8	-407.8
DMPA	**1**	1	-316.3	-316.3	-316.3	307.3			-307.3
	2	4	-400.6	-100.2	-200.3	79.1	386.4		-386.4
	3	5	-425.5	-85.1	-141.8	25.2	104.3	411.6	-411.6
Histamine	**1**	2	-304.9	-152.5	-304.9	295.1			-295.1
	2	4	-427.0	-106.8	-213.5	112.3	407.4		-407.4
	3	5	-462.6	-92.5	-154.2	34.4	146.7	441.8	-441.8
2-AEPip	**1**	1	-309.4	-309.4	-309.4	298.7			-298.7
	2	4	-402.1	-100.5	-201.0	84.0	382.7		-382.7
	3	5	-440.1	-88.0	-146.7	26.5	110.5	409.2	-409.2

It is observed that ΔE_{form} and E_b are bigger (more negative) for the 3:1 complexes. This indicates that 3:1 complexes are more stable and most likely to be present in solution, provided there are enough available amines. This agrees with the Yoe-Jones (29) experimental results. Cu(II) complexes are also more stable than Fe(II) complexes in all cases. On the other hand, the binding energies per bond E_b/N_b and per ligand E_b/N_l decrease (in absolute values) as the number of bonds and ligand number increases. This could be due to steric effects, and indicates the 3:1 complexes are the most labile and reactive.

In all cases, ΔE_1 is the lowest compared to ΔE_2 and ΔE_3, and the lowest ΔE_1 is by far the one corresponding to a 3:1 complex. This indicates that the prevalent mechanism for the reactions starts with the dissociation of one amine from a 3:1 complex, and if a dimer is formed from free amines, it is most likely to be with the first amine dissociated from another 3:1 complex. All this supports the proposed equations (1) and (2) from Scheme 1.

Cu(II) complexes have greater binding energies per amine than the corresponding Fe(II) ones, so they are less labile and reactive, consistently with experimental results that indicate that the reactions with Cu(II) complexes are slower than those with Fe(II) complexes. Nevertheless, it is noticeable that the overall energy differential for reactions (1) and (1) + (2) is smaller for Cu(II) complexes than for Fe(II) complexes.

The relative E_b/N_l for the different amine 3:1 complexes are: histamine >> DMPA $\geq$ 2-(AEPip) $\geq$ EDA for the Fe complexes, and histamine >> 2-AEPip > EDA > DMPA for Cu complexes. Histamine is the least labile and, therefore, the least reactive of all them, while the labilities of the other amine complexes are similar.

In Table 4, we show the covalent coordinated N-metal and hydrogen bonds present in the 3:1 complexes of histamine and 2-AEPip, having selected them as examples. The columns “Atom 1” and “Atom 2” show the bonded atoms and the bond type (see Figure 6). The calculated properties are: the relevant interatomic distance d, the angle α (in the case of H-bonds); AIM results for the bond critical point: electron density ρ, its Laplacian $\nabla^2(\rho)$, and its ellipticity ε; and the charge transference Δq of the bonded atoms, as described in the theoretical method section. Averages include the N-metal bonds only. For the complexes shown in the table, bond strengths, as inferred from the average bond distance, electron density at the BCP and charge transfer of the metal atom, are stronger for Cu complexes, showing the same trend in lability as the one inferred from the E_b/N_l value.

4. Conclusions

The present paper describes the kinetic determinations for ANS carried out with 1-chloro-2,4-dinitrobenzene, (DNClB), a good nucleofugue substrate, and several bifunctional amine coordination complexes with Cu(II) and Fe(II), in toluene. The amines selected as ligands were ethylenediamine (EDA), N,N-dimethyl propylamine (DMPA), histamine and 1-(2-aminoethyl)piperidine, 2-AEPip, because of their characteristics of bi-dentate ligands and the possible size of the metalo-cycle formed.

Table 4: N-metal coordinated bond characteristics. Bonded atoms, bond distance (Å), bond angle, electron density and its Laplacian at the BCP (au), ellipticity, and charge transfer (au) of the atoms. See abbreviations in the text.

atom 1...	**...atom 2**	**d**	**α**	**ρ**	**$\nabla^2(\rho)$**	**ε**	**Δq 1**	**Δq 2**
				Histamine-Fe(II)				
N1...	...Fe	2.294	-	0.04630	0.22044	0.495	-0.06643	-0.60252
N10...	...Fe	2.246	-	0.04985	0.24984	0.445	-0.13936	"
N19…	...Fe	2.296	-	0.04620	0.21951	0.508	-0.09042	"
N28…	...Fe	2.222	-	0.05393	0.24015	0.095	-0.15646	"
N36…	...Fe	2.318	-	0.04424	0.20869	0.552	-0.10294	"
N45…	...Fe	2.226	-	0.05353	0.23677	0.038	-0.16165	"
average		2.267		0.04901				
				Histamine-Cu(II)				
N1...	...Cu	2.124	-	0.06531	0.30644	0.022	-0.08142	-0.85221
N10...	...Cu	2.081	-	0.06935	0.34723	0.029	-0.14300	"
N19…	...Cu	2.095	-	0.07065	0.32166	0.018	-0.12443	"
N28…	...Cu	2.256	-	0.04741	0.23568	0.057	-0.15413	"
N45…	...Cu	2.098	-	0.06686	0.33444	0.077	-0.11363	"
N19-H...	...N36	1.959	176.5	0.03175	0.07933	0.006	-0.12443	-0.05705
average		2.131		0.06392				
				2-AEPip-Fe(II)				
N3...	...Fe	2.235	-	0.05734	0.23102	0.085	-0.14183	-0.65984
N9...	...Fe	2.259	-	0.05121	0.23932	0.434	-0.09320	"
N35…	...Fe	2.184	-	0.06027	0.27733	0.396	-0.11773	"
N54…	...Fe	2.241	-	0.05692	0.21930	0.044	-0.16076	"
N60…	...Fe	2.267	-	0.05006	0.23659	0.518	-0.09530	"
N29...	...H-N35	2.154	118.7	0.02444	0.07690	0.483	-0.02548	-0.11773
average		2.237		0.05516				
				2-AEPip-Cu(II)				
N9...	...Cu	2.393	-	0.03764	0.14861	0.028	-0.05443	-0.94867
N29…	...Cu	2.236	-	0.05393	0.22606	0.014	-0.08260	"
N35…	...Cu	2.086	-	0.07063	0.34286	0.017	-0.06654	"
N54…	...Cu	2.238	-	0.05381	0.22306	0.007	-0.09276	"
N60…	...Cu	2.026	-	0.08281	0.37628	0.009	-0.12789	"
N60-H…	...N3	1.859	175.0	0.04186	0.08409	0.010	-0.12789	-0.06871
average		2.196		0.05976				

DFT calculations were performed to determine the geometries and energies of the complexes, considering one to three ligands. Results indicate that the most stable complexes are those with three amine molecules, while those with Cu(II) are more stable than those of Fe(II) in all cases. The binding energy of the amine-complexes, which correlates with other bond strength indicators, was found to be determinant in the reaction rate, and it correlates satisfactorily with the order of reactivity observed in the kinetic experiments, which indicate that histamine complexes are least reactive, and Cu(II) complexes are less reactive than their Fe(II) counterparts. The studied amine structures were quantum-chemically calculated in previous works and in the present study several H-bonds pattern were found in the complexes as well.

Finally, we believe that other effects that influence the different lability of complexes are the stereo electronic and chelating effects of the different ligands, both attributed to the structure of each amine, and to the existence of intra- or intermolecular hydrogen bonds.

Regarding the biological interest in the mechanism of action of metallo species chelated to peptides and other amine containing groups, if the studied system is considered as a simplified model, it can be concluded that the amine-metal complexes should partly dissociate prior to reaction with a potential biological site in a lipophilic media.

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References

(1) Abdel-Mohsen Ebain Nassr, L. *Int. J. Chem. Kinet.* 2010, 42, 372-379 and referentes therein.

(2) Muñoz, V. A.; Ferrari, G. B.; Sancho, M. I.; Montaña, M. P. *J. Chem. Eng. Data* 2016, 61, 987-995.

(3) El-Subruit, G. M.; Younes, G. O.; Zeitouni, F. S.; Amira, M. F. *Int. J. Chem. Kinet*. 2008, 40, 416-422.

(4) Escudero, D.; González, L. J. *Chem. Theory Comput*. 2012, 8, 203-213.

(5) Shubina, V. S.; Kozina, V. I.; Shatalin, Yu. V. *Russian Journal of Bioorganic Chemistry* 2017, 43, 463-470.

(6) Shehata, A. K.; Fathalla, M.; Header, H. M. A.; Hamed, E. A. *Int. J. Chem. Kinet*. 2012, 44, 27-40.

(7) von Zelewsky, A. *Stereochemistry of Coordination Compounds*, John Wiley, Chichester, England, 1995.

(8) Sivaraj, K.; Elango, K. P. *J. Solution Chem*. 2010, 39, 1681-1697.

(9) Nie, H.-J.; Yang, W.-W.; Zheng, R.-H.; Shi, Q.; Chen, H.; Yao, J.; Zhong, Y.-W. *Inorg. Chem.*, 2015, 54, 1272-1282.

(10) Nelson, D. L.; Cox, M.; Lehninger *Principles of Biochemistry*, 7thed., W. H. Freeman & Co (Sd), USA, 2017.

(11) Campbell, N. R.; Hasinoff, B. *British Journal of Clinical Pharmacology* 1991, 31, 251-255.

(13) Al Zoubi, W.; Al-Hamdani, A. A. S.; Ahmed, S. D.; Ko, Y. G. *J Phys Org Chem*. 2018, 31, e3752. https://doi.org/10.1002/poc.3752.

(14) Ejidike, I. P.; Ajibade, P. A. *Molecules* 2015, 20, 9788-9802.

(15) Nudelman, N. S.; *ANS Reactions of Amines in Aprotic Solvents in The Chemistry of Amino, Nitroso, Nitro and Related Groups Supplement F2*, Eds. S. Patai, John Wiley & Sons, Ltd, London, UK, 1996.

(16) a) Alvaro, C. E. S.; Nudelman, N. S.; *ARKIVOC*, 2003, 10, 95-106. b) Nudelman, N. S.; Alvaro, C. E. S.; Yankelevich, J. S. *J. Chem. Soc. Perkin Trans*. 2, 1997, 2125-2130.

(17) a) Alvaro, C. E. S.; Bergero, F. D.; Bolcic, F. M.; Ramos, S. B.; Nudelman, N. S. *J. Phys. Org. Chem.* 2016, 29, 565-573. b) Alvaro, C. E. S.; Nudelman, N. S.; *Trends in Org. Chem*. 2011, 15, 95-107, and references therein.

(18) Alvaro, C. E. S.; Nudelman N. S. *Phys. Chem. Special Issue: Chemical Kinetics* 2013, 3, 39-47.

(19) Alvaro, C. E. S.; Nudelman, N. S., *Int. J. Chem. Kinet.* 2010, 42, 735-742.

(20) Nudelman, N. S., Alvaro, C. E. S. *J. Phys. Org. Chem.* 2011, 24, 1067-1071.

(21) Bergero, F. D.; Alvaro, C. E. S.; Nudelman, N. S., Ramos de Debiaggi, S. *J. Mol. Struct. (Theochem)* 2009, 896, 18-24.

(22) Bergero, F. D.; Alvaro, C. E. S.; Nudelman, N. S.; Ramos de Debiaggi, S. J. *Argent. Chem. Soc*. 2013, 100, 35-47.

(23) Parr, R. G.; Yang, D.; *Density- Functional Theory of Atoms and Molecules*, Ed. Oxford University Press, New York, 1989.

(24) a) Becke, A. D. *J. Chem. Phys*. 1993, 98, 5648.5652. b) Lee, C.; Yang, C. W.; Parr, R. G. *Phys. Rev. B*, 1988, 37, 785-793.

(25) Schwöbel, J.; Ebert, R.-U.; Kühne, R.; Schürmann, G. *J. Chem. Inf. Model*. 2009, 49, 956-962.

(26) Ribeiro, R. F.; Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. *Phys. Chem. Chem. Phys*. 2011, 13, 10908-10922.

(27) Bader, R. F. W. *Chem. Rev.* 1991, 91, 893-928.

(28) Shaker, A. M.; Abdel-Mohsen Ebain Nassr, L.; Adam, M. S. S.; Mohamed, I. M. A. *Russian Journal of General Chemistry*, 2014, 84, 2037–2042.

(29) Yoe, J. H.; Jones, A. L. *Ind. Eng. Chem. Anal*. Ed. 1944, 16, 111–115.

(30) Stewart, J. P. *J. Mol. Model*. 2007, 13, 1173-1213.

(31) Kanal, Y.; Keith, J.; Hutchison, G., *Int. J. Quantum Chem*. 2018, 118, (5), e25512.

(32) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A. et al. Gaussian 09, Revision A.01, Gaussian, Inc., Wallingford CT, 2009.

(33) a) Scherlis, D. A.; Estrin, D.A., *Int. J. Quantum Chem.* 2002, 87, 158-188, and references therein. b) Conry, R. R. “Copper: Inorganic & Coordination Chemistry”. *Encyclopedia of Inorganic Chemistry*, First Edition. Wiley, 2006.

(34) a) Feller, D. J. Comp. Chem. 1996, 17, 1571-1586. b) Schuchardt, K. L.; Didier, B. T.; Elsethagen, T.; Sun, L.; Gurumoorthi, V.; Chase, J.; Li, J.; Windus, T. L. *J. Chem. Inf. Model* 2007, 47, 1045-1052.

(35) Boys, S. F.; Bernardi, F. *Mol. Phys.* 1970, 19, 553-556.

(36) Lu, T.; Chen, F. Multiwfn: A multifunctional wavefunction analyzer. *J. Comput. Chem.* 2012, 33, 580-592.

(37) Parthasarathi, R.; Subramanian, V.; Sathyamurthy, N. *J. Phys. Chem. A* 2006, 110, 3349-3351.

(38) Reiners, M.; Maekawa, M.; Daniliuc, C. G.; Freytag, M.; Jones, P. G.; White, P. S.; Hohenberger, J.; Sutter, J.; Meyer, K.; Maron, L.; Walter, M. D. *Chem. Sci.* 2017, 8, 4108-4122.