

Research Article

New Vibrational Information on Simple Amides in Solution: A Case Study on GaCl₃-Formamide Complexes

Anna K. M. S. Gomes and Wagner A. Alves 

Departamento de Química Inorgânica, Instituto de Química, Universidade Federal do Rio de Janeiro, Caixa Postal 68563, Rio de Janeiro, RJ 21941-909, Brazil

Correspondence should be addressed to Wagner A. Alves; wagner@iq.ufrj.br

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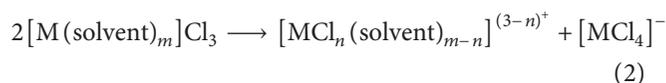
IR and Raman measurements were carried out for GaCl₃-formamide (FA) solutions, and comparisons with the Al³⁺ and Fe³⁺ chemistry are presented. Upshifts of both ν_{CO} and ν_{CN} modes of FA are observed, and analyses of the corresponding bands suggest different types of solvatocomplexes. The twisting mode (ν_{HNH}) of FA at 1190 cm⁻¹, which is IR- and Raman-inactive, is activated only in the former upon coordination to high electrostatic potential ions. The spectral behavior exhibited in this region is shown for the first time in the literature and has helped in the understanding of the coordinated FA structure. The catalytic power of Ga³⁺ towards amide bond hydrolysis is also predicted for the first time using vibrational spectroscopy and may be useful for biological studies.

1. Introduction

Although gallium does not have a known role in normal cellular physiology, the discovery of gallium-based compounds for use in diagnostic and therapeutic medicine has led several workers to investigate its biological mechanism of action, and the solvates formed especially at near neutral pH [1]. The *in vivo* behavior of Ga³⁺ could be better understood from comparisons with Al³⁺ and Fe³⁺ because of their ionic and covalent bonding characters [2, 3]. Indeed, Ga³⁺ ([Ar] 3d¹⁰) shares certain chemical properties with Fe³⁺ ([Ar] 3d⁵) that enable the former to be taken up by tumor cells and microorganisms as an iron mimetic. For instance, their similar sizes and absence of crystal field stabilization energy (high-spin Fe³⁺) are some of the parameters to be deemed in ion transport and cellular uptake processes [1]. Similarities between Al³⁺ ([Ne]) and Ga³⁺ are also expected because both chemical elements belong to the group 13 in the periodic table.

The solvation structures formed in the solutions of these ions have not been yet fully understood. One particularly insidious problem is related to extensive and complicated

hydrolysis reaction, which leads to uncertainties about the total coordination number and inner- and outer-shell solvation extent, and such limitations have been associated to the slow formation, aging, and agglomeration of hydrolytic polymers [4, 5]. An alternative to overcome these obstacles is the use of nonaqueous solvents because the salts of these ions are in general more stable than in water. In fact, Ga³⁺, Al³⁺, and Fe³⁺ chlorides form a variety of soluble complexes according to the following steps:



where M = metal; m and n (≤ 3) vary as a function of the salt composition. Hence, $[\text{MCl}_4]^-$ is practically the major component in these solutions, as very well established by calorimetric and vibrational spectroscopic studies [3, 6]. The abundance of this tetrahedral species seems to be dependent not only on the kind of metal ion but also on the nature of the solvent. For example, the 348 cm⁻¹ band, assigned to the

A_1 mode of $[\text{AlCl}_4]^-$, is present in the Raman spectra of AlCl_3 -tetrahydrofuran (THF) solutions at room temperature [6], but no signal can be detected at this region as the ether is replaced by formamide (FA) [7]. On the contrary, FeCl_3 -FA solutions show the arising of the 332 cm^{-1} band, which is due to A_1 vibration of $[\text{FeCl}_4]^-$ [8]. In common, the addition of Al^{3+} and Fe^{3+} chlorides to the FA solvent causes upshifts of both ν_{CO} and ν_{CN} modes, instead of the behavior typically observed as simple amides coordinate other ions and produce the ν_{CO} downshift and the ν_{CN} upshift [8–15].

So far, we have observed that the two spectral patterns of FA show good relationship with the electrostatic potential of coordinated ions, ϕ , and with the catalytic activity of metals toward amide bond cleavage reactions [15]. In other words, metal ions with ϕ values between 1.95 and $3.59 \times 10^{20}\text{ J}\cdot\text{C}^{-1}$ cause ν_{CO} downshift and ν_{CN} upshift and may be deemed as catalysts. On the contrary, ϕ values $\geq 3.91 \times 10^{20}\text{ J}\cdot\text{C}^{-1}$ are relative to ions which provoke upshifts of both ν_{CO} and ν_{CN} vibrations, and the rate of cleavage products is extremely low. Hence, based on this information as well as on the similarities and differences found for Al^{3+} and Fe^{3+} , GaCl_3 -FA solutions were investigated by vibrational spectroscopy in order to broaden our knowledge on the solvation structures. In addition, the catalytic power of Ga^{3+} is predicted for the first time on the basis of our methodology, and such type of information may be valuable for biological studies focusing on metal-catalyzed peptide hydrolysis processes.

2. Methodology

2.1. Reactants and Sample Preparations. Formamide (Sigma-Aldrich) was distilled under reduced pressure, discarding the first and last portions of distillate. Gallium chloride (Sigma-Aldrich) was used without any further purification, but its addition to the solvent was carried out in a controlled N_2 atmosphere dry box. All solution contents are expressed as molalities (mol kg^{-1}).

2.2. Experimental Details. Raman spectra were acquired on a Bruker SENTERRA confocal Raman microscope, equipped with a thermoelectrically-cooled CCD detector and a 20x long working-distance objective (Olympus) with numerical aperture equal to 0.4. The 532 nm line of a diode laser delivering 20 mW power at the sample was used for excitation. The samples were accommodated in NMR tubes, and the acquisition time for each spectrum was 60 s per window. IR measurements were carried out on a Nicolet FT-IR Magna 760 spectrometer using NaCl windows. Both Raman and IR spectra were obtained with 4 cm^{-1} resolution at the temperature of $20 \pm 2^\circ\text{C}$. OMNIC 7.3 software was employed for the spectral data treatment, and details can be found in our previous works [6–8, 10–15].

3. Results and Discussion

Raman spectra of FA and its solutions with variable contents of GaCl_3 are shown in Figure 1. The effect of the salt addition on the solvent spectrum is characterized by the arising of new bands at 1747, 1355 cm^{-1} , and others below 600 cm^{-1} . The assignment of the FA bands for the corresponding

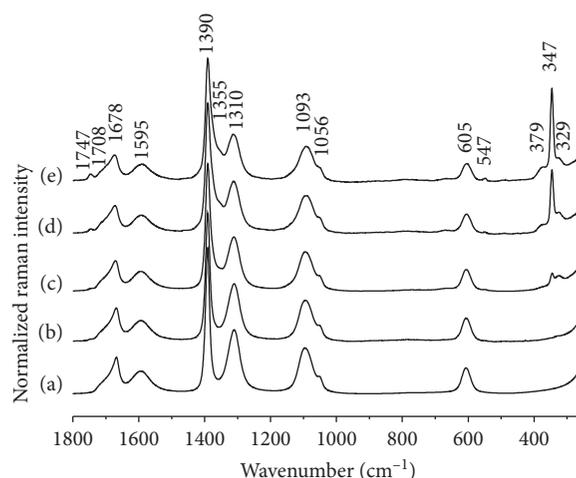


FIGURE 1: Raman spectra of liquid FA and its solutions containing GaCl_3 at different molalities: (a) solvent; (b) 0.1; (c) 0.5; (d) 1.0; (e) 1.5.

spectral range has been reported in a recent work and references therein [15]. Undoubtedly, upshifts of the ν_{CO} and ν_{CN} modes of FA, originally identified at 1705/1675 and 1310 cm^{-1} , are observed in the presence of the solute and so may be assigned to the respective vibrations of FA coordinated to Ga^{3+} , similarly to Al^{3+} and Fe^{3+} chemistry. Concerning the features in the low wavenumber region, a detailed discussion will be presented later.

We have not yet reported any IR spectrum for FA solutions containing ions which provoke the aforementioned upshifts, but a recent experimental and theoretical study on Ca^{2+} -FA complexes shows useful information on the band activity at the ν_{CO} region by using Raman and IR spectra [16]. In light of those results, a comparison between such techniques is then illustrated in Figure 2 for the ν_{CO} and δ_{HNNH} regions. The curve fittings reveal that only three bands can be extracted from Raman and IR spectra of the solvent, and their positions are practically identical, except for their intensities which depend on the selection rules of each technique. The CO stretching mode of H-bonded FA molecules in different environments produces bands at around 1710 and 1678 cm^{-1} , whereas the $\sim 1600\text{ cm}^{-1}$ band corresponds to amino group bending. Besides them, a fourth feature at 1749 cm^{-1} is present in the IR spectrum acquired for the most concentrated GaCl_3 solution, and its relationship with the Raman band at 1747 cm^{-1} is out of discussion. The larger intensity of this latter indicates that the electromagnetic radiation significantly polarizes the CO group due to the greater participation of π electrons, and the reinforcement of this oscillator is fully justified by the upshift of the corresponding band.

Since the spectral changes observed at the solvent region are consistent with the coordination phenomenon, it would be now advisable to determine the average number of FA molecules around Ga^{3+} ($n_{\text{FA-Ga}}$) in order to obtain information on the geometry of the complexes, which is a key stage for the calculation of the ϕ values. For doing this, both ν_{CO} and ν_{CN} regions were employed and due to the good relationship between the non-coordinated amide bands, and

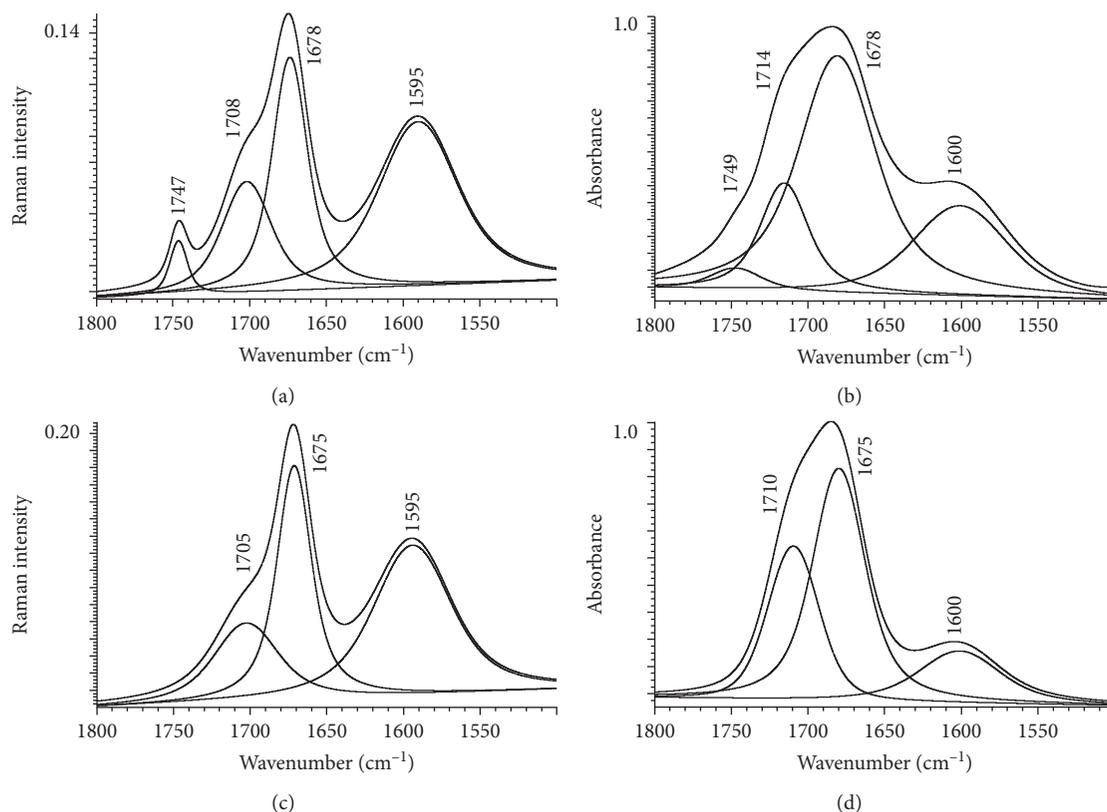


FIGURE 2: Curve-fitting analyses for Raman (a) and IR (b) spectra of liquid FA (c) and a 1.5 mol·kg⁻¹ GaCl₃ solution (d) at the ν_{CO} and δ_{HNH} regions.

the salt content, $n_{\text{FA-Ga}}$ was determined following the equation [6–8, 10–15]:

$$I_o = -n_{\text{FA-Ga}}J_o b_{\text{Ga}} + J_o b_{\text{FA}}, \quad (3)$$

where I_o corresponds to the integrated intensities of the non-coordinated FA bands at ~ 1675 and 1310 cm⁻¹, J_o is the specific intensity of each one, and b is the solution content. The equation (3) shows that I_o may change as a linear function of b_{Ga} as $I_o = ab_{\text{Ga}} + \beta$. The effect of the salt content on the ν_{CO} and ν_{CN} bands of non-coordinated FA is clearly seen in Figure 3, where the trend is quite similar, and the plot of I_o against b_{Ga} gives a straight line, indeed. Furthermore, the I_o behavior at both spectral regions suggests that there is no contribution of coordinated amide molecules, in contrast to what was reported by Ohashi and coworkers from theoretical vibrational spectra [16]. Values of $n_{\text{FA-Ga}}$ equal to 1.5 and 2.0 were found for Ga³⁺ at the respective ν_{CO} and ν_{CN} regions and suggest that complexes containing from 1 to 2 FA molecules in the inner-solvation sphere of the metal ion are the most abundant in the media. The coordination must occur through the O atom due to the appearance of a band at 547 cm⁻¹ (Figure 1), which is located at the region characteristic of the $\nu_{\text{Ga(III)-O}}$ vibration [17, 18]. Similarly, a band at 545 cm⁻¹ was identified in the Raman spectra of FeCl₃-FA solutions and assigned to the $\nu_{\text{Fe(III)-O}}$ mode [8]. On the contrary, the $\nu_{\text{Al(III)-O}}$ and $\nu_{\text{Al(III)-N}}$ vibrations gave rise to the respective bands at 547 and 295 cm⁻¹ and suggested bidentate coordination of FA, in which the chelating effect

was responsible for the high stability of the complex [7]. In fact, distortions in the FA shell were proposed only for temperatures higher than 100°C , where a new band belonging to $[\text{AlCl}_4]^-$ showed up in the Raman spectra. In the present work, the formation of $[\text{GaCl}_4]^-$ is evidenced by the signals at 379 and 347 cm⁻¹ (Figure 1), which are typically assigned to its T_2 and A_1 modes, respectively [19, 20]. Similar to Fe³⁺ chemistry, such a tetrahedral unit is spontaneously formed in the FA solutions along with cationic species (reaction (1)).

The spectral features related to the major complexes are shown in Figure 4, and their assignment is also made on the basis of $n_{\text{FA-Ga}}$ determined at the ν_{CO} and ν_{CN} regions. A closer look in the Raman spectrum of the most diluted salt solution reveals the presence of a 329 cm⁻¹ band (Figure 4(a)), whose position is practically identical to that reported for AlCl₃.THF [21] and [AlCl₃(THF)₃] [6]. This unique signal is then ascribed to the $[\text{GaCl}_3\text{FA}]$ complex not only by analogy with the former but also due to the good relationship with $n_{\text{FA-Ga}}$. In other words, FA is capable of dissociating the Ga₂Cl₆ dimer (equilibrium (1)), which is abundant in the solid state, but only one molecule penetrates into the coordination sphere of the metal. This seems to be true because no band corresponding to $[\text{GaCl}_4]^-$ is seen at this composition and such an interpretation is very well supported by the reaction (2). The most intense band of this anion (A_1 mode) begins arising in the spectra from the 0.3 molal concentration on (Figures 4(b)–4(f)), along with another at 319 cm⁻¹ which may be attributed to

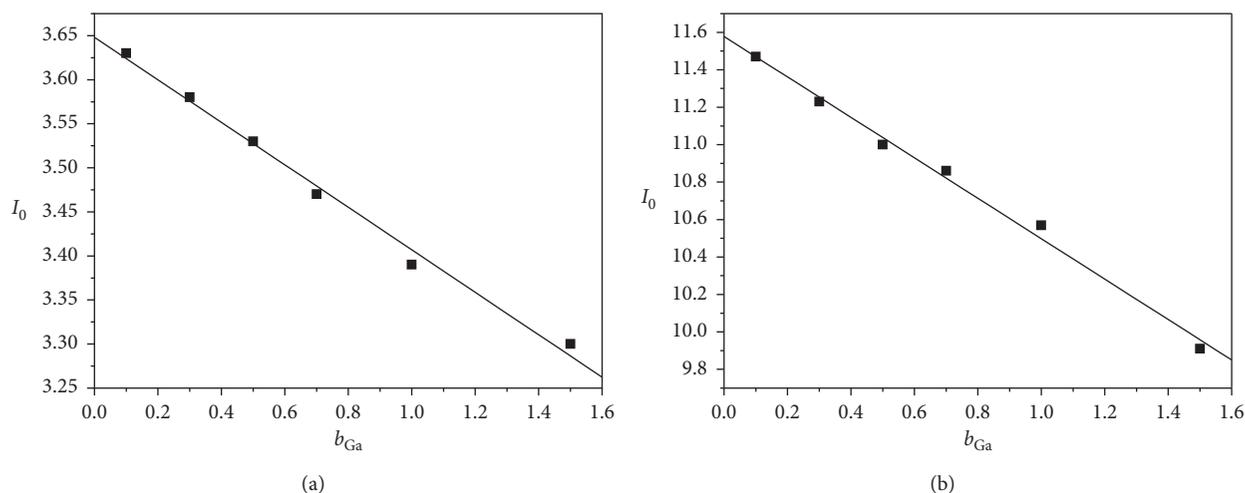


FIGURE 3: Typical plot of I_0 against b_{Ga} for the CO (a) and CN (b) stretching bands of non-coordinated FA molecules.

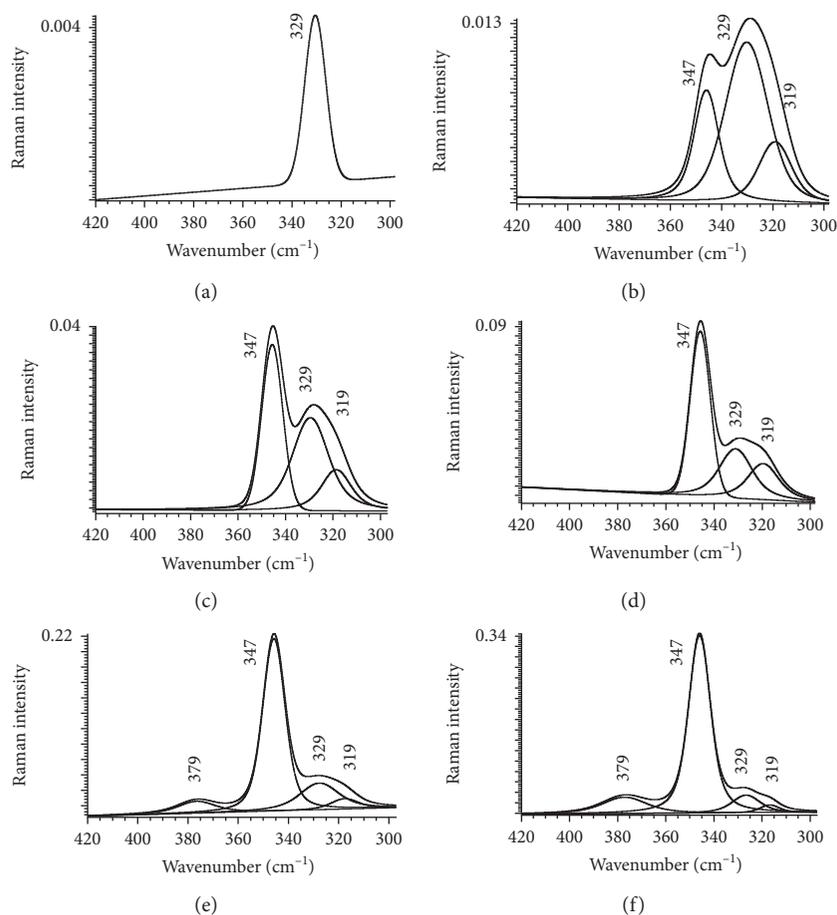


FIGURE 4: Raman spectra of GaCl_3 -FA solutions at different molalities at the region characteristic of the metal-chloride vibrations: (a) 0.1; (b) 0.3; (c) 0.5; (d) 0.7; (e) 1.0; (f) 1.5.

$[\text{GaCl}_2(\text{FA})_2]^+$ according to $n_{\text{FA-Ga}}$ as well. However, the bands belonging to the complexes with one and two FA molecules have their intensities reduced, whereas the T_2 mode, which is the weakest signal of $[\text{GaCl}_4]^-$, can be now seen at higher salt contents. Such a trend suggests that

other complexes may also exist in these solutions in order to maintain the neutrality of the system. Despite this possibility, the aforementioned tetrahedral species seem to be majority in the media, and this geometry provides a ϕ value for Ga^{3+} equal to $4.42 \times 10^{20} \text{ J}\cdot\text{C}^{-1}$, which is as high

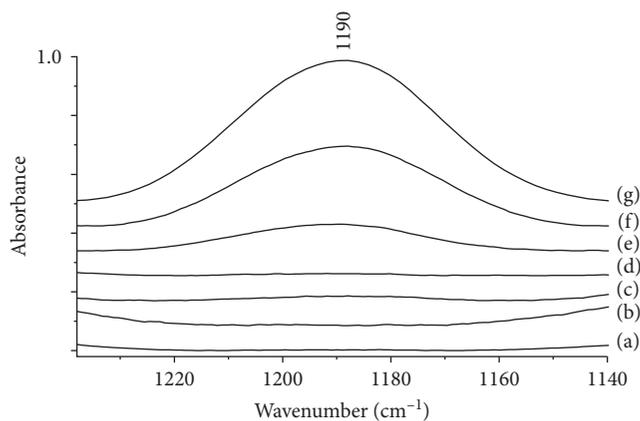


FIGURE 5: IR spectra of liquid FA and 0.5 mol·kg⁻¹ salt solutions at the ν_{HNH} region: (a) solvent; (b) Zn(II); (c) Ni(II); (d) Co(II); (e) Fe(III); (f) Al(III); (g) Ga(III).

as the ones determined for Al³⁺ and Fe³⁺ [15] and is in excellent agreement with our interpretation for the upshifts of the ν_{CO} and ν_{CN} modes.

We also noticed that the upshifts of the ν_{CO} and ν_{CN} bands are always observed in the IR and Raman spectra along with the twisting mode (γ_{HNH}), which is inactive in both spectra of liquid FA [22]. Figure 5 clearly shows the activation of the corresponding band at 1190 cm⁻¹ in the IR spectra of FA solutions containing higher ϕ ions, in contrast to the behavior exhibited by ions whose ϕ values vary from low to moderate. The activated band may be due to the structure of FA coordinated to the first set of ions, which must possess a pyramidal NH₂ moiety and so yield a relatively high electrical dipole along this group. On the contrary, the electromagnetic radiation is not able to substantially induce such a vector and give rise to a band in the Raman spectra of the Ga³⁺ solutions (Figure 1). Although pyramidalization of the amine group has been interpreted as an indication of FA coordination through the N atom [16], the $\nu_{\text{Ga(III)-N}}$ vibration, which is typically observed at 372 cm⁻¹ [23] cannot be identified in the spectra up to 0.7 mol·kg⁻¹ and if present at higher salt contents, it is overlapped by the T_2 mode of [GaCl₄]⁻ (Figure 4).

4. Conclusion

Upshifts of both ν_{CO} and ν_{CN} modes of FA were observed in the presence of a Ga³⁺ salt, similar to Al³⁺ and Fe³⁺ chemistry. Such atypical shifts strongly suggest that the coordinated FA structure differs from the one commonly reported in the literature for simple amides, which causes the ν_{CO} downshift and the ν_{CN} upshift in the IR and Raman spectra. By combining band analyses of these modes with the region characteristic of the $\nu_{\text{Ga(III)-Cl}}$ vibrations, it was possible to determine that [GaCl₃FA], [GaCl₂(FA)₂]⁺, and [GaCl₄]⁻ are the most abundant complexes in the studied molality range. The presence of the latter may be an indication of FA coordination through the O atom, even though a second FA molecule might use the N atom to coordinate the metal ion, in contrast to the Al³⁺ chemistry where

complexation *via* both O and N atoms avoided its formation at room temperature.

The activation of the γ_{HNH} mode in the IR spectra of GaCl₃-FA solutions was interpreted on the basis of the pyramidalization of the amino group, and such a finding was complemented by the ν_{CO} band of coordinated FA, whose Raman intensity is larger as compared with the IR one. Hence, a pyramidal FA structure containing π electrons over the CO oscillator could be the reason for stabilization of a species little sensitive to the nucleophilic attack, as expected due to the presence of a high ϕ ion. Although gallium compounds are of interest in the tumor treatment, our methodology points out to low catalytic activity of this metal towards peptide hydrolysis reactions.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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