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Real-time Raman monitoring of dry media heterogeneous alkylation of imidazole with acidic and basic catalysts

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ABSTRACT

The *N*-substitution of heterocycles, e.g., imidazole, is a key route to prepare important bactericidal compounds and new drugs; these are also precursors for the synthesis of ionic liquids, which are very promising as an alternative to conventional organic solvents. Controlling alkylation of imidazoles to a monoalkylation is challenging due to the tendency of bis-alkylation leading to the formation of ionic liquids (ILs; imidazolium salts). Raman spectroscopy provides a real-time non-invasive insight during reaction in the presence of acidic or basic catalysts. 2-Methylimidazole is first alkylated to 1-butyl-2-methylimidazole, but alkylation reaction continues with either catalyst; 2-methylimidazole to *N*-alkyl-2-methylimidazole, *N*-alkyl-2-bromo-2-methyl-2,3-dihydro-1*H*-imidazole, *N*-alkyl-2-methylimidazolium bromide and 1,3-dialkyl-2-methylimidazolium bromide following different alkylation mechanism. We report here the use of *in situ* Raman during dry media *N*-alkylation of 2-methylimidazole with 1-bromobutane in the presence of both acid and basic heterogeneous catalysts. Real-time Raman spectroscopy allows determining when monoalkylation is completed and suggesting different reaction pathways for bis-alkylation towards the ILs formation. This feature underlines the great potential of Raman spectroscopy for reaction investigation and process monitoring.

1. Introduction

N-Substituted imidazoles and their derivatives (Fig. 1) are pharmaceutically important due to their pharmacodynamic properties (antiparasitic, antifungal and antimicrobial activity) [1]. In the last two decades the interest for the study of this group of pharmaceuticals has grown due to the increase of infections with fungic origin, caused by the massive employment of new drugs (antibiotics, corticosteroids and immunosuppressant) as well as for the employment of surgical aggressive technologies (catheterisms, transplants, prosthesis.) and the appearance of new diseases as those caused by the virus of the human immunodeficiency (HIV). In an industrial process-development environment, it is sometimes necessary to take a strictly empirical approach to optimize yield and reaction times. For *N*-alkylimidazole, an additional alkylation would form imidazolium ionic liquids (ILs) (e.g., 1,3-disubstituted imidazolium cations) [2,3]. The ionic liquid synthesis requires 1-alkylimidazole compounds as starting material and only a limited range of these compounds are commercially available besides being relatively expensive.

Solid acids and bases are commonly used for the manufacture of fine chemicals by catalyzing, e.g., alkylation reactions [5,6], determining different reaction pathways. In the case of nitrogen heterocycles *N*-alkylations, several solid acid catalysts such as alumina and zeolites have been proposed and also solid bases as clays and alkali doped carbons [7,8,1(a)] due to the convenience and environmental-friendly characteristic of solid catalysts. Both acid- and base-catalyzed alkylation of 2-methylimidazole yield the *N*-alkyl-2-methylimidazole following a different mechanism of imidazole alkylation (Schemes 1 and 2).

Monitoring heterocycle alkylation reaction traditionally requires parallel analyses by chromatography, however, these are time consuming and may not provide direct real-time analysis of reaction progress nor they can provide molecular knowledge on reaction mechanism and intermediates. Vibrational spectroscopies are particularly valuable to monitor and investigate reactions in the liquid phase, provide real-time and more detailed information than those demanding additional processes, e.g., chromatography. Infrared and Raman spectroscopies are most valuable vibrational techniques. Infrared works best on an absorption configuration, where it is quantitative and provides excellent quality spectra.

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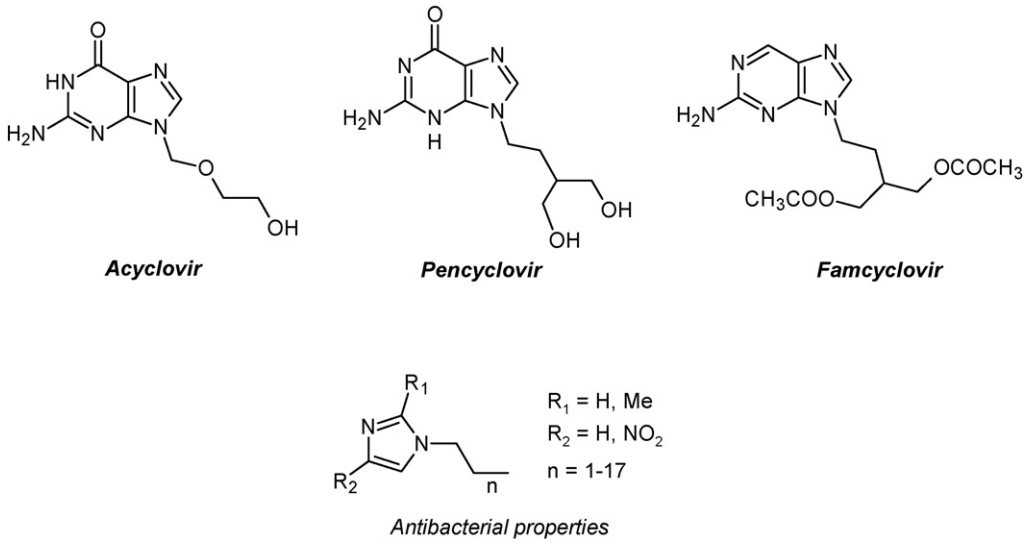
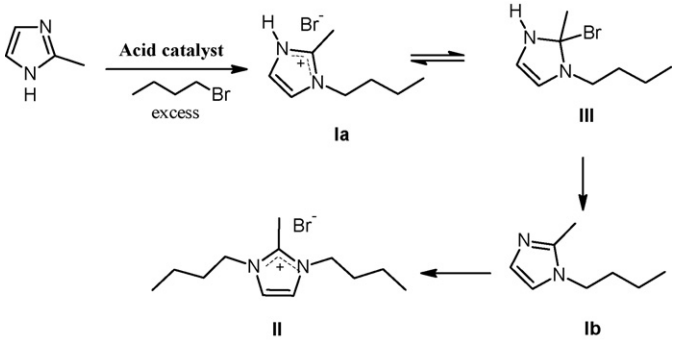


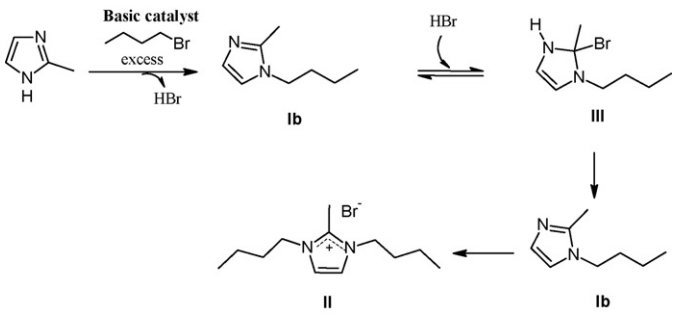
Fig. 1. *N*-alkylimidazoles with pharmacological activity.

However, real-time analyses during reaction in liquid phase are hampered by interference by solvent in aqueous media reaction, and chemical requirements of spectroscopic windows, and temperature. Significant progress has been made in the use of attenuated-total reflection for liquid phase analyses. On the other hand, Raman works with scattered radiation, and typically uses visible radiation, which simplifies analyses through highly inert optic windows (quartz, sapphire) that possess excellent mechanical properties. It is not limited by the temperature of the sample or by the presence of water as a solvent. A number of works illustrate the detailed insight into reaction progress details [12]. Raman spectroscopy is a powerful non-invasive tool for real-time *in situ* monitoring of organic reactions [4] when the reactants, products or intermediates are Raman active and are present in adequate concentrations. With this system, any liquid phase reaction can be monitored, even in the presence of a solid catalyst.

Imidazoles are well known to Raman spectroscopy: already, in the 1960s, Josien and his co-workers [9] published a comprehensive work about infrared and Raman spectroscopy of imidazole and its deuterated derivatives. In this paper, we report the use of Raman monitoring of the synthesis of 1-alkyl-2-methylimidazoles under both acid and basic heterogeneous media. This methodology can be applied to multiple reactions in the preparation of other *N*-alkylated purines that serve as precursors in the primary route to pharmaceutically important acyclic nucleoside analogues with antiviral properties such as pencyclovir, acyclovir and famcyclovir by substitution of adenine with different alkylating agents [1(a)]. Furthermore we also monitor during the synthesis the formation of the corresponding ionic liquid with potential industrial applications; 1-alkyl-2-methylimidazole and 1,3-dialkyl-2-methylimidazolium bromide (Schemes 1 and 2).



Scheme 1. Mechanism of *N*-alkylation of imidazolic rings with alkyl halides in acid media.



Scheme 2. Mechanism of *N*-alkylation of imidazolic rings with alkyl halides in basic media.

2. Experimental

Mixture of 2-methylimidazole (5 mmol) and 1-bromobutane (12 mmol) was heated in a batch reactor and in absence of any solvent at 333 K under vigorous stirring using an excess of the alkylating agent and both acid and basic solid catalysts (0.1 g), hydrated niobia $Nb_2O_5{\cdot}nH_2O$ [10] and Cs-Norit activated carbon [11]. The reaction procedure was as follow; imidazole and the corresponding catalyst (sieved to particle size ranging from 0.074 to 0.140 mm

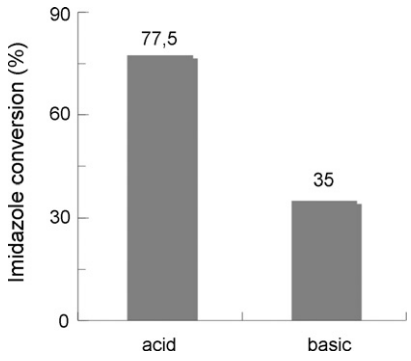


Fig. 2. Imidazole conversion values at 4 h reaction time, 333 K.

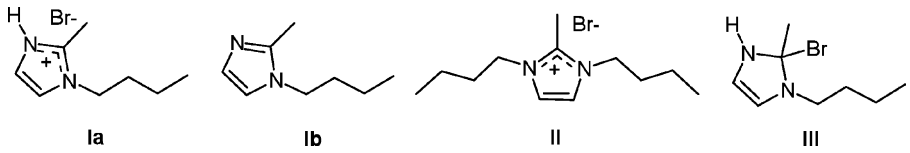


Fig. 3. Reaction products for the alkylation of imidazole with *n*-bromobutane.

in diameter) were mixed in a Pyrex flask and heated in an oil bath at 333 K. After that 1-bromobutane was added in absence of any solvent and reaction time started.

To check the absent of external and internal diffusion problems, we carried out a series of experiments using imidazole and 1-bromobutane over the corresponding catalyst changing the stirring rates (1000 and 3500 rpm) and the particle size (≤0.074, ≤0.14, and ≤0.25 mm in diameter). The results obtained indicate that, in this range of conditions, the reaction is neither under external nor internal diffusion control [10,11].

The reaction was continuously monitored by Raman spectroscopy with an immersion probe fitted to a PerkinElmer Raman

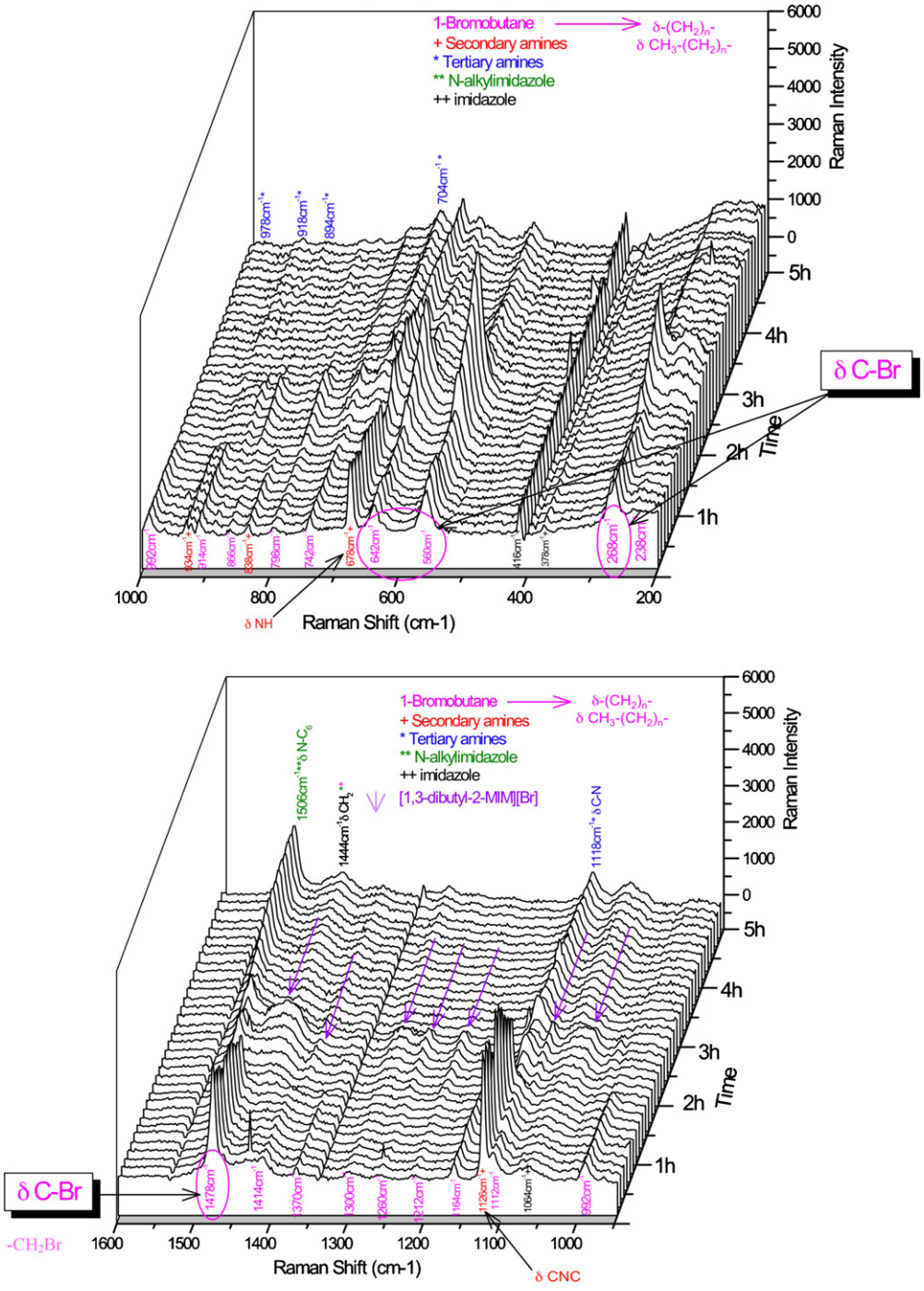


Fig. 4. Raman spectra of the *N*-alkylation of 2-methylimidazole with 1-bromobutane at 333 K using an acid solid catalyst; $Nb_2O_5 \cdot nH_2O$.

Station 400-F system using 100 mW of 785 nm excitation line; spectra were acquired every 5 min, each spectrum consisted of 50 accumulations of 1 s. The intensity of the Raman bands was ratioed to that of the imidazole ring at 416 cm^{-1}, which is not affected by the reaction. Activity was also measured by gas chromatography in a HP-5890 GC fitted to a 50 m long ultra 2–5% phenyl methyl siloxane capillary column and a flame ionization detector (FID). Samples were taken periodically with acetone (20 mL) and filtered with a filter Millipore syringe. The final reaction products, after completion of the reaction (5 h in acid catalyst and 6 h in basic catalyst) were identified and quantified by ^{1}H NMR analyses.

NMR spectra were recorded with a Bruker DRX-400 (400.13 MHz for ^{1}H, and 100.033 MHz for ^{13}C). ^{1}H chemical shifts (δ) in DMSO-d_6 or CD_3COCD_3 are given from internal tetramethylsilane. The reaction product ratios were determined from the corresponding signals assigned to CH_2-N groups for each product.

3. Results and discussion

Gas chromatography analyses in Fig. 2 apparently indicate that 1-butyl-2-methylimidazole product forms with 100% selectivity in the presence of both acid and basic heterogeneous catalysts, reaching 77.5 and 35.0% of imidazole conversion, respectively, at 4 h reaction time and 333 K.

Interestingly, ^{1}H NMR analyses after reaction indicate that 1-butyl-2-methylimidazole is not the only reaction product. ^{1}H NMR spectra of the reaction crudes using DMSO-d_6 as solvent showed the presence of three singlets at δ 2.62, 2.58 and 2.55, assignable to methyl groups over the heterocyclic ring. This circumstance demonstrates that the alkylation of 2-methylimidazole using the experimental conditions mentioned above lead to the formation of three different reaction products; signals corresponding to *N*-alkyl-imidazoles can be also observed in the aromatic region in

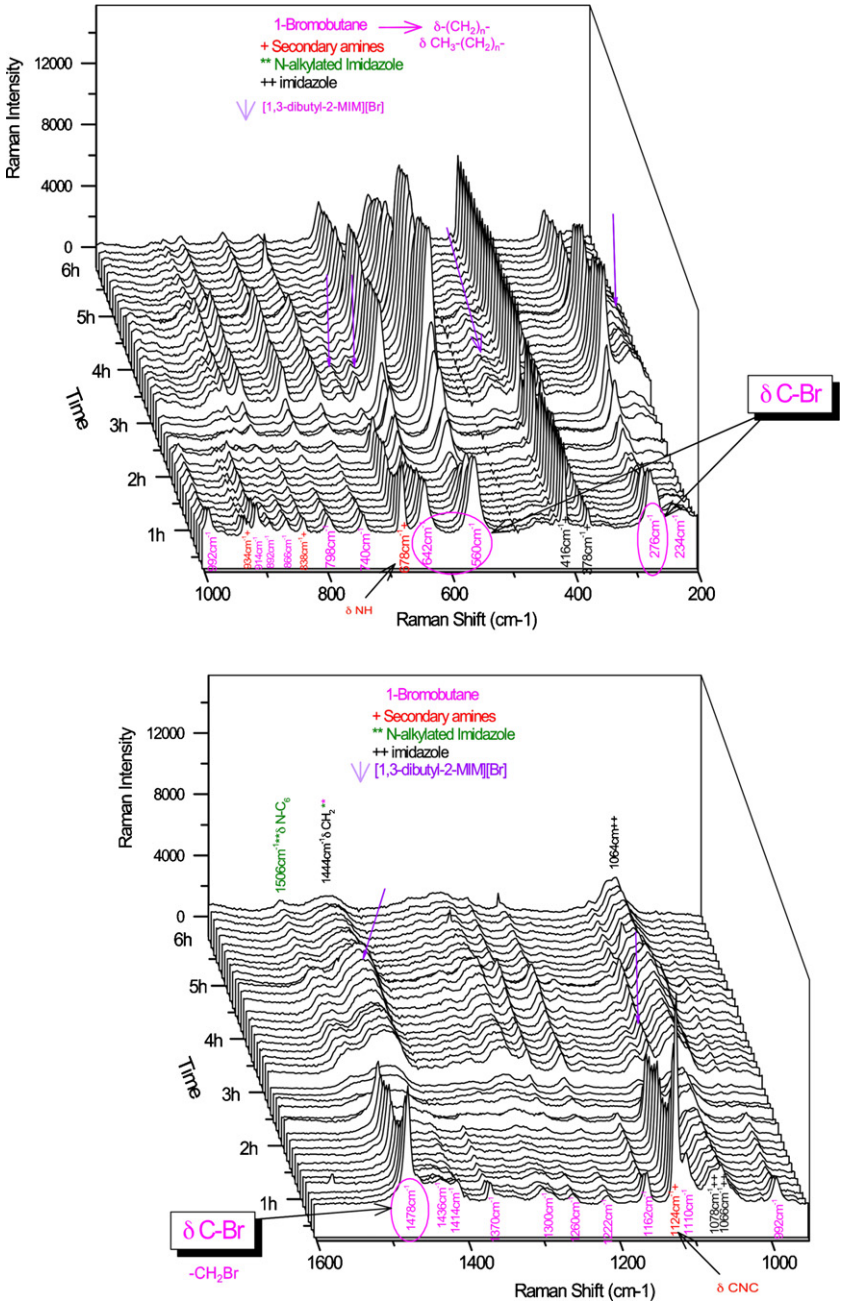


Fig. 5. Raman spectra of the *N*-alkylation of 2-methylimidazole with 1-bromobutane at 333 K using a basic solid catalyst; Cs-Norit.

the spectrum. With these data in mind, the structures **I** and **II** are assigned to two of the reaction products for alkylation of imidazole with *n*-bromobutane (Fig. 3). Note that when using $Nb_2O_5{\cdot}nH_2O$ as catalyst, the reaction product was **Ia** (broad singlet at δ 14 corresponding to NH group in the NMR spectrum), while compound **Ib** was observed when using Cs-Norit carbon.

In order to elucidate the structure for the third product, we particularly analyzed by NMR the crude from the reaction catalyzed by $Nb_2O_5{\cdot}nH_2O$ using CD_3COCD_3 as solvent. In such case, in the ^1H NMR spectrum, besides the signals corresponding to methyl and aromatic protons, appear two triplets at δ 4.36 and 4.24, with coupling constants of 7.5 Hz, assigned to CH_2-N groups for the compounds **Ia** and **II**, respectively. Furthermore, the presence of a multiplet at 3.63–3.51 ppm corresponding to two protons could be probably assigned to the CH_2-N groups in compound **III**, as tentative structure in accordance with Raman spectroscopy data.

Fig. 3 depicts the possible structures of the alkylated products as function of the used catalyst; while the reaction catalyzed by $Nb_2O_5{\cdot}nH_2O$ yielded a mixture of the compounds **Ia**, **II** and **III** in 33:53:14 ratio, in the case of using Cs-Norit activated carbon a mixture of **Ib**, **II** and **III** (31:33:36) was observed.

Indeed, ^1H NMR confirms that 2-methylimidazole is monoalkylated to 1-butyl-2-methylimidazole. However, ^1H NMR also indicates that it is further alkylated affording 1,3-dibutyl-2-methylimidazolium bromide. The use of acidic or basic catalyst results in different product distribution.

Raman spectra during reaction provide a real-time molecular insight on the reaction progress. Figs. 4 and 5 illustrate representative Raman spectra during reaction in the presence of acidic and basic catalysts, respectively. The $-CH_2-$ deformation vibration peaks at 1350–1500 cm^{-1}, corresponding to the saturated bromomethyl group of the 1-bromobutane reactant, decreases during reaction time. Raman spectra follow the consumption of $-CH_2Br$ (1478 cm^{-1}) and C–Br (642, 560 and ~270 cm^{-1}) deformation vibration peaks of 1-bromobutane. For both catalysts, the Raman bands corresponding to $-CH_2Br$ vibrations disappear with reaction time; whereas C–Br characteristic bands decrease reaching a minimum at 1.5 h of reaction time.

Concomitantly, the transformations in the imidazole ring become apparent. On one side, the consumption of N–H deformation vibration peak near 678 cm^{-1} reflects the progressive consumption of the secondary amine group of 2-methylimidazole. On the other side, the C–N stretching vibrations in the nitrogen heterocyclic ring with a secondary amine (838, 934 and 1124 cm^{-1}) decrease in intensity. Complementary to it, representative Raman bands in the range 800–1200 cm^{-1} and the band at 1506 cm^{-1} due to C–C–N deformation vibration and C–N stretching in the *N*-alkylated (tertiary amine) nitrogen heterocyclic ring of the product grow stronger.

In both cases, the band at 678 cm^{-1} due to N–H deformation vibration intensity pass through a minimum during the first hour and a half of reaction time. Its increase at longer reaction times could be probably due to the formation of 1-butyl-2-bromo-2-methylimidazole (**III**). In the presence of an acidic catalyst, it may also be because 1-alkylated imidazolic ring remains protonated affording the corresponding protic ionic liquid, 1-butyl-2-methylimidazolium bromide (**Ia**), probably in equilibrium with compound **III** (Scheme 1). Raman spectroscopy data are in good agreement with ^1H NMR analyses. The loose of one molecule of HBr in **Ia** and subsequent alkylation lead to the formation of the quaternary salt, 1,3-dibutyl-2-methylimidazolium bromide **II**. Concomitantly, representative Raman bands in the range 800–1200 cm^{-1} (C–C–N deformation vibration) and the band at 1506 cm^{-1} (C–N stretching) of the *N*-alkylated nitrogen heterocyclic ring of the 1-alkylated and 1,3-dialkylated products grow stronger. This is consistent with the formation of the quaternary

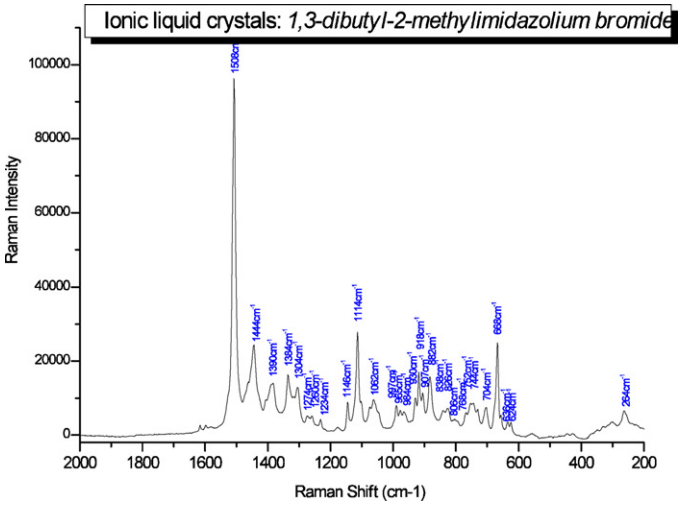


Fig. 6. Raman spectrum of 1,3-dibutyl-2-methylimidazolium bromide ionic liquid.

1,3-dialkyl-2-methylimidazolium bromide salt **II**, where the Br anion would be vibrating with the carbon in position 2 of imidazolic ring causing an increase in C–Br intensity bands (Scheme 1, Figs. 4 and 5).

Both catalysts, acidic and basic, generate similar spectral features during the first 1.5 h (Figs. 4 and 5); in line with GC analyses, Raman spectra indicate that reactants consumption is faster in the presence of an acid catalyst than in the presence of a basic catalyst. Raman spectral features become significantly different at longer reaction times. The Raman bands of the *N*-alkylated imidazole grow faster in the presence of an acid catalyst. The appearance of new bands in the range 1450–1000 cm^{-1}, characteristic of the 1,3-dialkyl-2-methylimidazolium quaternary salt are more evident in acid media, as compared with reference in Fig. 6.

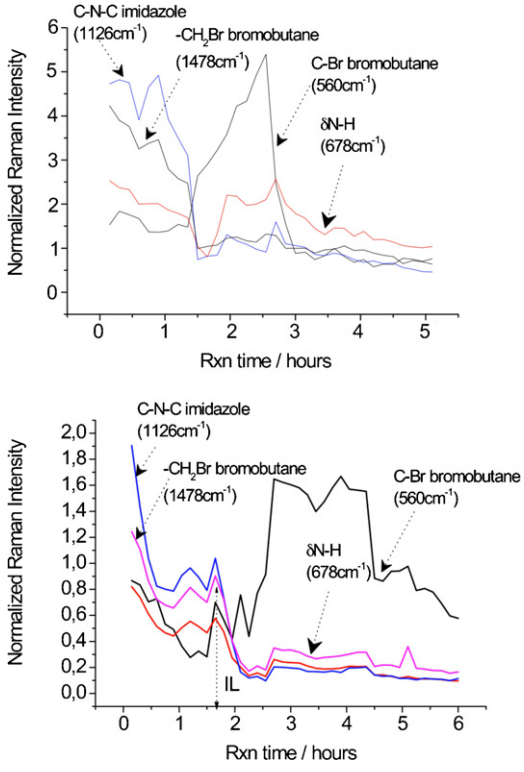


Fig. 7. Characteristic vibrations of reactants imidazole and 1-bromutane in acid media (up) and in basic media (down).

The disagreement between gas chromatography data and those of Raman and ^{1}H NMR spectroscopy must be due to the experimental characteristics of gas chromatography, GC analyses do not detect the formation of 1-butyl-2-bromo-2-methylimidazole (**III**) and neither the corresponding protic ionic salt and quaternary salt, 1-butyl-2-methylimidazolium (**Ia)** and 1,3-dibutyl-2-methylimidazolium bromides (**II**), respectively. These structures have high boiling point and just break down into 1-butyl-2-methylimidazole and 2-methylimidazole structures at the GC injector. Raman spectroscopy and RMN analyses confirm the formation of these products.

Real-time assessment of single *N*-alkylation is fundamental for an efficient synthesis of pharmaceutical precursors, avoiding over-alkylation. The representation of the intensities of representative Raman bands is illustrated in Fig. 7 shows how Raman evidences the time for complete alkylation of imidazole, preventing further alkylation into ionic liquid phase. Raman intensity trends show that maximum conversion to monoalkylated imidazole happens at ca. 1.5 h in acidic medium and at ca. 2.25 h in basic medium. The dialkylation to imidazolium salts after monoalkylation has been done is significantly faster and more important in acidic medium.

4. Conclusion

Single alkylation of 2-methylimidazole is a convenient procedure to prepare pharmaceuticals to treat a variety of infections, but the tendency to bis-alkylation limits its selectivity and it must be controlled. Chromatographic off-line analyses provide inaccurate results while spectroscopic measurement like ^{1}H NMR and Raman are sensitive to all reaction products and do not affect their structure.

Monitoring liquid phase organic reactions by Raman spectroscopy provides real-time molecular insight, which will be critical to optimize them to improve the synthesis of *N*-substituted imidazoles intermediates as 1-butyl-2-methylimidazole with pharmacological properties. Imidazole alkylation may form the protic ionic liquid, 1-butyl-2-methylimidazolium bromide, and the quaternary salt, 1,3-dibutyl-2-methylimidazolium bromide, with important industrial applications.

Real-time Raman spectroscopic monitoring during alkylation reaction provides thorough molecular information on the reaction mechanism and possible intermediates, while remains non-invasive. Thus, it is possible to see progressive dry media alkylation on 2-methylimidazole at *N*-position in the presence of either acidic or basic catalysts. This methodology can be applied to an unlimited number of processes. This is critical to understand reaction mechanisms and provides a tool for real-time reaction monitoring and reaction control.

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