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NMR Characterization of Hydrate and Aldehyde Forms of Imidazole-2-carboxaldehyde and Derivatives

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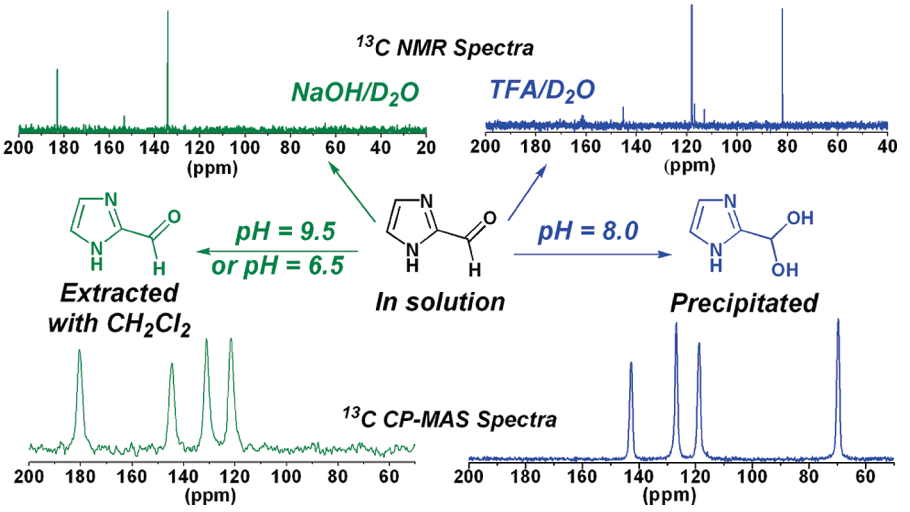

The existence and stability of the aldehyde-hydrate form of imidazole-2-carboxaldehyde (**4**) were studied using FTIR together with solution- and solid-state NMR experiments. The results allowed us to conclude that the hydrate form was stable and precipitated at pH = 8.0 and that the aldehyde form was isolated at pH = 6.5 and 9.5. Moreover, the presence of the aldehyde-hydrate form was studied through NMR experiments in D_2O at both alkaline and acidic pH. In addition, the tautomeric forms of the 2-substituted imidazole compounds were also analyzed to investigate the influence of the hybridization on the carbon adjacent to the imidazole ring, by ^{13}C NMR in DMSO-d_6, acetone-d_6, and $CDCl_3$. The presence of the *syn*- and *anti*-isomers of oxime **8** obtained from **4** were characterized by solid-state NMR and variable-temperature NMR experiments in acetone-d_6.

1. Introduction

The few stable crystalline hydrates known (such as the hydrate forms of cyclopropanone and polychlorinated aldehydes and ketones) are those that have a strongly electronegative group associated with the carbonyl group since, in general, the hydrates can seldom be isolated because they readily revert to the parent aldehyde.[1−3] In particular, chloral hydrate is a stable crystalline substance because, in order to revert to chloral, a water molecule must be left out, and this is difficult by the electron-withdrawing character of the Cl_3CR group.[4] Specifically, in the solid state, the sodium pyruvate is in the ketone form, whereas the lithium pyruvate takes the *gem*-diol form.[5] These forms have been studied by

(1) Schulman, E. M.; Bonner, O. D.; Schulman, D. R.; Laskovics, F. M. *J. Am. Chem. Soc.* **1976**, *98*, 3793–3799.
(2) Gambaryan, N. P.; Rokhlin, E. M.; Zeifman, Y. V.; Ching Yun, C.; Knunyants, I. L. *Angew. Chem., Int. Ed.* **1966**, *5*, 947–956.
(3) Krois, D; Lehner, H. *Monatsh. Chem.* **1982**, *113*, 1019–1024.
(4) Luknitskii, F. L. *Chem. Rev.* **1975**, *75*, 259–289.
(5) Hanai, K.; Kuwae, A.; Sugawa, Y.; Kunimoto, K. K.; Maeda, S. *J. Mol. Struct.* **2007**, *837*, 101–106.

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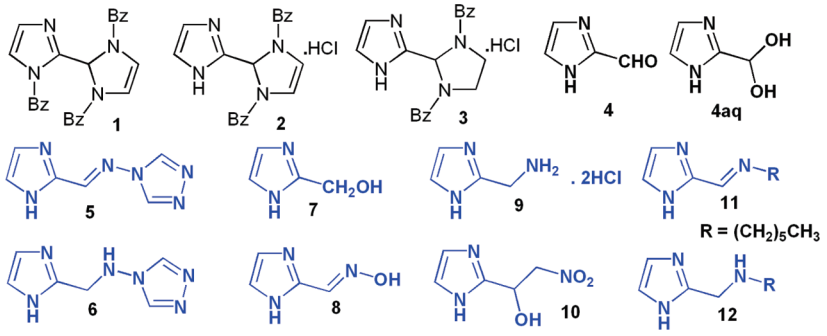
SCHEME 1. Chemical Structures of 2-Substituted Imidazole Derivatives



solid-state ^{17}O NMR, which is a useful tool to prove the tautomeric form of the α-keto functional group commonly found in intermediates of enzymatic reactions.[6] In addition, the hydrate, keto, and enol forms of oxalacetic acid have been studied by ^{13}C NMR in the solution state.[7]

In particular, the imidazole-2-carboxaldehyde (**4**) is an important reagent in the synthesis of active compounds. In this field, imidazole derivatives bearing chiral carbinamine structures with relevance in medicinal chemistry,[8] thiosemicarbazone complexes for the search of new therapeutic agents,[9] substituted quinoline derivatives with anti-breast cancer activity,[10] and some semicarbazones with antimicrobial activity have been synthesized from **4**.[11]

On the other hand, tautomerism in five-membered heterocyclic compounds has been studied in a variety of ways because of its importance in the reactivity of compounds in chemical processes and its effect on biological systems.[12−14] In particular, Hollstein et al. have studied how the temperature, solvents, concentration, and size of the substituent on 2-substituted imidazoles and benzimidazoles can have effects on tautomerism.[12] In imidazole molecules, the hydrogen atom may be bound either to the N_1 (1H form) or to the N_3 atom (3H form) of the aromatic ring as a consequence of the prototropic tautomerism at nitrogen atoms.

The aim of the present work was to study the existence and stability of the aldehyde-hydrate form of **4**, by using spectroscopic techniques in the liquid and solid states. We also carried out studies in 2-substituted imidazole derivatives in order to study the influence of hybridization on the carbon adjacent to the imidazole ring in the tautomeric process.

2. Results and Discussion

2.1. NMR and FTIR Studies of Imidazole-2-carboxaldehyde (4) and Its Hydrate Form (4aq). In the present work **4** was synthesized following the report of Godefroi et al. (Scheme 1, **1**−**4**).[15] Scheme 1 also shows the 2-substituted imidazole derivatives studied in the present work.

In the synthetic route reported by Godefroi et al., **3** is treated in hydrochloric acid for 22 h and is then isolated and precipitated with $NaHCO_3$ solution (pH = 8.0) in order to obtain **4** (Scheme 1).[15] However, instead of this, according to our results, the compound obtained was the aldehyde-hydrate form (**4aq**) in the solid state and the aldehyde form (**4**) in the solution state (Figure 1). Interestingly, in compound **4**, the signal corresponding to the carbon of the carbonyl group at 181.3 ppm, present in the ^{13}C NMR spectrum in DMSO-d_6 or D_2O/NaOH (Figure 1), was absent in the ^{13}C CP-MAS spectrum (Figure 1c). In addition, a new resonance peak at 69.6 ppm appeared in the solid-state spectrum assignment to the carbon of the *gem*-diol.

Next we decided to study which medium favors the existence of the aldehyde (**4**) or the hydrate (**4aq**) from the mixture reaction after the hydrolysis of **3**. With this aim, we changed the pH of the resulting solution after the hydrolysis of **3** to either 9.5 or 6.5 (Scheme 2). Afterward, we were successful in extracting **4** from the mixture at both pHs using an apparatus for continuous extraction with methylene chloride, indicating that **4** was soluble around the pH at which **4aq** precipitated. The FTIR results for the solids obtained from aqueous solutions at pH = 6.5 and 9.5 with CH_2Cl_2 demonstrate that both compounds presented the carbonyl stretching at 1685 cm^{-1} and the same FTIR spectra, in contrast with the solid at pH = 8.0. The FTIR spectrum of the solid **4aq** showed the stretching of the C−O bond at 1084 cm^{-1} and the deformation in the plane of the C−O−H at 1287 cm^{-1} among other bands. In addition, the FTIR-ATR spectrum of the corresponding solution of the solid **4aq** dissolved in methanol showed that this compound evolved completely to the aldehyde form, in agreement with the results obtained from the ^{13}C NMR in D_2O or DMSO-d_6 (Figure 1 and Supporting Information).

To confirm the structure of **4aq** after the synthetic process, we performed a $^1H-^{13}C$ HETCOR NMR experiment in the solid state (Figure 2). The 2D spectrum reveals clear and resolved correlations between carbons and their bound (A, B, and C correlations) or neighboring protons (D and E correlations). Additionally, the presence of a resonance signal at 10.3 ppm in the ^1H spectrum can be assigned to a R-OH proton. This kind of proton, as well as protons from

(6) Zhu, J.; Geris, A. J.; Wu, G. *Phys. Chem. Chem. Phys.* **2009**, *11*, 6972–6980.
(7) Buldain, G.; De los Santos, C.; Frydman, B. *Magn. Reson. Chem.* **1985**, *23*, 478–481.
(8) Perl, N. R.; Leighton, J. L. *Org. Lett.* **2007**, *9*, 3699–3701.
(9) Casas, J. S.; Castiñeiras, A.; Rodríguez Argüelles, M. C.; Sánchez, A.; Sordo, J.; Vázquez López, A.; Vázquez López, E. M. *Dalton Trans.* **2000**, *14*, 2267–2272.
(10) Shi, A.; Nguyen, T. A.; Battina, S. K.; Rana, S.; Takemoto, D. J.; Chiang, P. K.; Huaa, D. H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 3364–3368.
(11) Rodríguez Argüelles, M. C.; Mosquera Vázquez, S.; Sanmartín Matalobos, J.; García Deibe, A. M.; Pelizzi, C.; Zani, F. *Polyhedron* **2010**, *29*, 864–870.
(12) Papadopoulos, E. P.; Hollstein, U. *Org. Magn. Reson.* **1982**, *19*, 188–191.
(13) Minkin, V. I.; Garnovskii, A. D.; Elguero, J.; Katritzky, A. R.; Denisko, O. V. *Adv. Heterocycl. Chem.* **2000**, *76*, 157–323.
(14) Dolzhenko, A. V.; Pastorin, G.; Dolzhenko, A. V.; Chui, W. K. *Tetrahedron Lett.* **2009**, *50*, 2124–2128.
(15) Bastiaansen, L. A. M.; Van Lier, P. M.; Godefroi, E. F. *Organic Synthesis*; Wiley: New York, 1990; Collect. Vol. VII, pp 287−290.

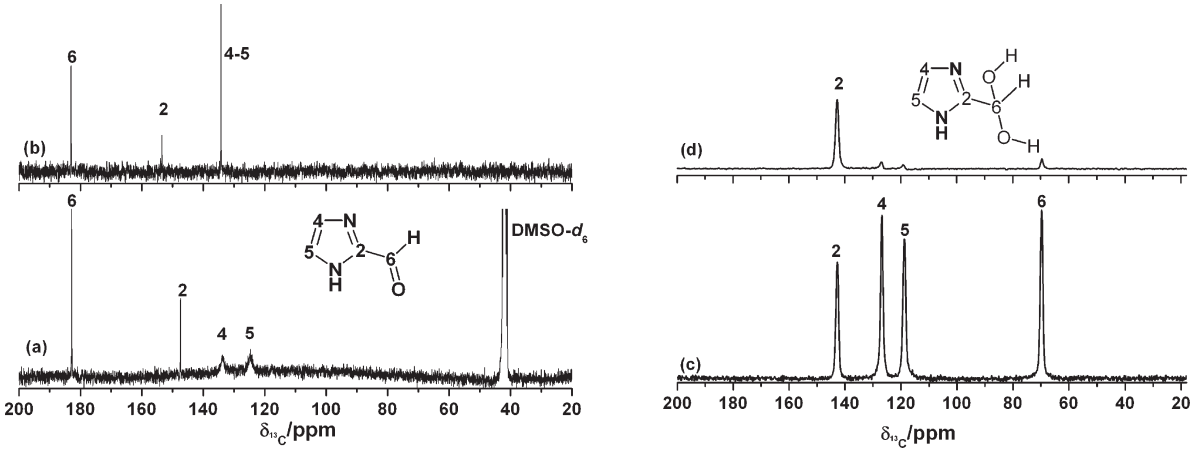


FIGURE 1. ^{13}C NMR spectra in DMSO-d_6 (a) and D_2O/NaOH (b) of **4** and ^{13}C CP-MAS (c) and NQS spectra (d) of **4aq**. The inset shows the carbon numbering used throughout the text for the ^{13}C spectra.

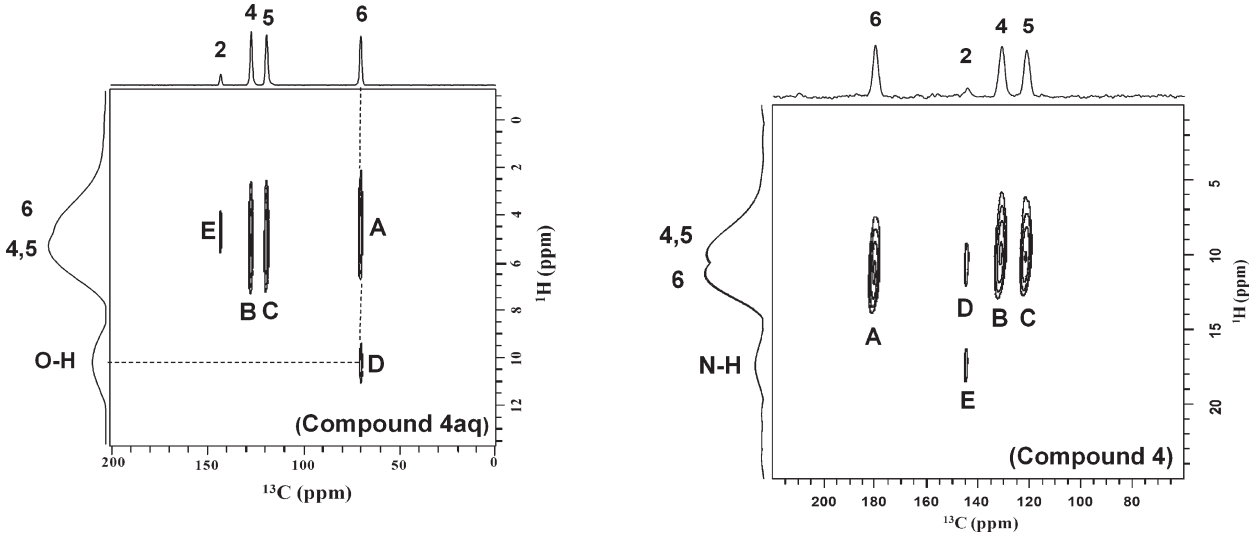
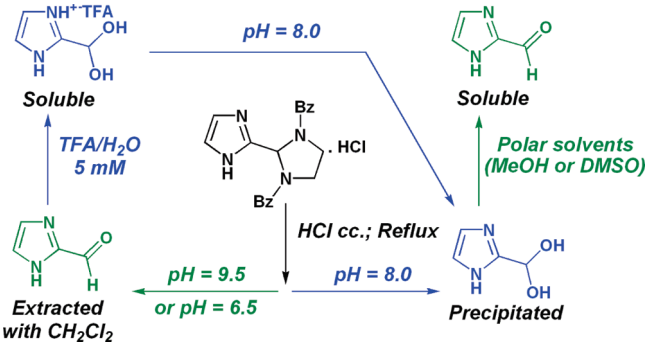


FIGURE 2. $^1H-^{13}C$ HETCOR spectra of compounds **4aq** and **4** in the solid state. Proton and carbon projections together with their assignments are indicated in each dimension.

SCHEME 2. Experimental Conditions That Favor the Aldehyde or the Hydrate Form of 4



carboxylic acids, are not usually seen in solution experiments because of a high degree of exchange.[16] Interestingly, this proton is correlated with C_6, which in addition presents a clear correlation with another proton at 4.7 ppm (H_6), supporting our conclusion that **4** was obtained as the aldehyde-hydrate form **4aq**. Remarkably, the HETCOR spectrum of **4** showed new correlations in comparison with the 2D spectrum of **4aq** (Figure 2). In particular, C_2 presented a correlation with the R-NH proton at 17.4 ppm (E), besides the interaction with the aldehydic hydrogen at 11.3 ppm (D).

Then, to study the existence of the hydrate **4aq** in acidic solution, we obtained ^1H and ^{13}C NMR spectra of **4** in 5.44 M TFA/D_2O (Figure 3). Interestingly, it was possible to demonstrate that **4** evolved completely to **4aq** taking into account the presence of the proton at 6.15 ppm and the absence of the aldehydic proton at 9.63 ppm. Moreover, the ^{13}C NMR spectrum presented a carbon resonance at 82.0 ppm and not the carbon at around 180 ppm, which finally demonstrated that the hydrate form can be obtained in acidic solution.

Possibly the electron withdrawing of the imidazolium cation, which was generated in acidic conditions, may explain the stability of the *gem*-diol form in **4aq**. However, the solubility of either **4** or **4aq** was dependent on the pH of the

(16) Romañuk, C. B.; Manzo, R. H.; Garro Linck, Y.; Chattah, A. K.; Monti, G. A.; Olivera, M. O. *J. Pharm. Sci.* **2009**, *98*, 3788–3801.

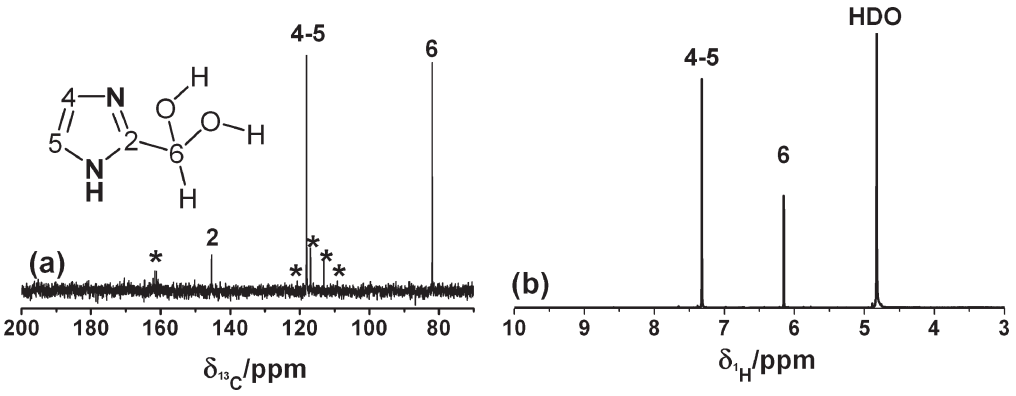


FIGURE 3. ^{13}C (a) and ^{1}H NMR spectra (b) of **4** in 5.44 M of TFA/D_2O. The asterisks in the ^{13}C NMR spectrum are for the TFA carbon resonances.

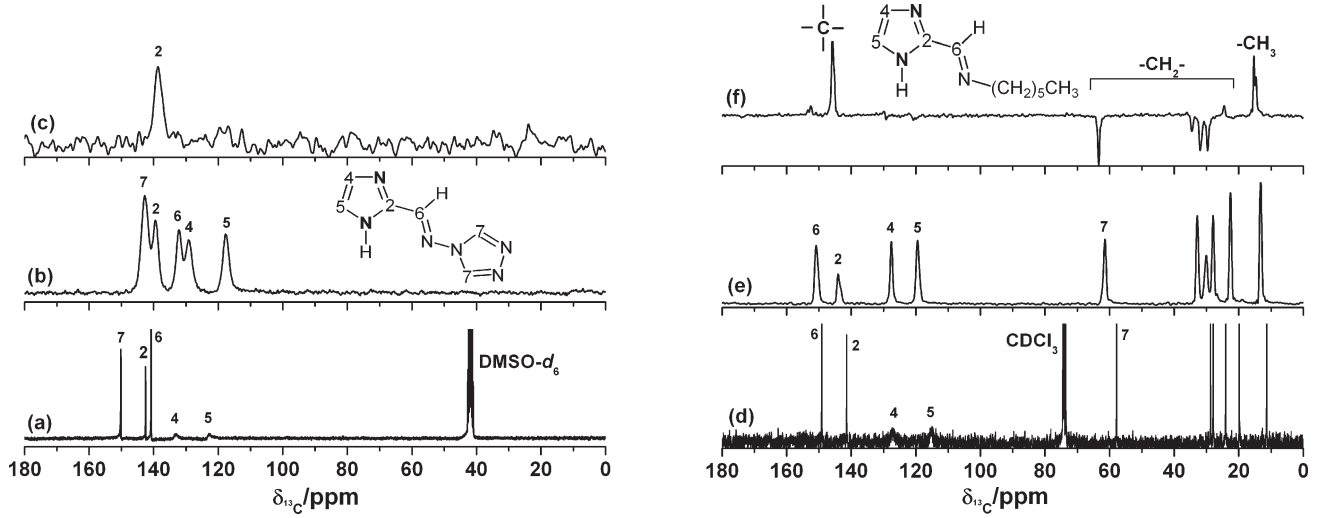


FIGURE 4. ^{13}C NMR spectra of **5** in DMSO-d_6 (a) and CP-MAS (b) and NQS spectra (c) and ^{13}C NMR spectra of **11** in $CDCl_3$ (d) and CP-MAS (e) and CPPI spectra (f).

medium, taking into account the acid−base properties of the imidazole ring (Scheme 2).

Finally, we can summarize that the addition of water to the carbonyl group in **4** was analogous to hemiacetal formation and that it was catalyzed in acidic medium, precipitating the stable hydrate form at pH = 8.0. As a result, the carbonyl form in solution can be extracted with Cl_2CH_2. In basic medium we did not observe the presence of **4aq** in solution according with the NMR experiments in D_2O/NaOH (Figure 1). Scheme 2 states the experimental conditions in order to summarize which medium favors the forms **4** or **4aq**.

2.2. NMR Studies in 2-Substituted Imidazoles. The NMR experiments in all compounds were measured in the order of 0.15 M and at 298 K. In the synthesized derivatives (**4**, **5**, **8**, **11**), the nonmagnetic equivalence of C_4 and C_5 arose from a low tautomeric equilibrium between 1H and 3H forms in solution, in the NMR time scale, giving rise to the same number of signals as in the solid-state ^{13}C spectra (Figures 1, 4 and 5). Tautomeric exchange is practically stopped in the solid state as a result of the loss of molecular symmetry. In the case of compounds **4**, **5**, and **11**, ^{13}C CP-MAS spectra revealed well-resolved peaks for the C_{4-5}. In the ^{13}C spectra of the same compounds in solution (Figures 1, 4, and 5), the signals corresponding to the mentioned carbons arose as two broad peaks with intensity lower than that of the quaternary carbon (C_2). In contrast, **4** in D_2O/NaOH or D_2O/TFA presented one well-resolved signal for C_{4-5} as a consequence of the fast proton transfer enhanced by the medium (Figure 1 and 3). Also, **2**, **3**, and **9** in DMSO-d_6 showed equivalence for C_{4-5} as a result of the protonation of the imidazole ring during their synthetic process (see Supporting Information).

An important fact to take into account in **4**, **5**, **8**, and **11** was the hybridization at the C_6. When the hybridization at the mentioned carbon was sp^2, two signals were observed in the ^{13}C spectra for C_{4-5} in DMSO-d_6 or $CDCl_3$ (Figures 1, 4, and 5). However, if the hybridization at C_6 was sp^3, only one resonance signal was present for C_{4-5}, as in the case of compounds **6**, **7**, **10**. and **12** (Figure 5 and Supporting Information). Previous studies of tautomerism in azoles have used aprotic polar deuterated solvents (HMPT (hexamethylphosphoramide), DMF, and DMSO) in order to reduce the rate of tautomeric exchange.[17,18] However, our results showed that the DMSO-d_6 solvent did not substantially affect the proton transfer between the molecular associations of imidazole molecules in comparison with **11** in $CDCl_3$. In relation to **12** in $CDCl_3$, the ^{13}C NMR spectrum was in

(17) Chenon, M. T.; Coupry, C.; David, M.; Grant, D. M.; Pugmire, R. J. *J. Org. Chem.* **1977**, *42*, 659–661.
(18) Toppet, S.; Wouters, G.; Smets, G. *Org. Magn. Reson.* **1978**, *11*, 578–579.

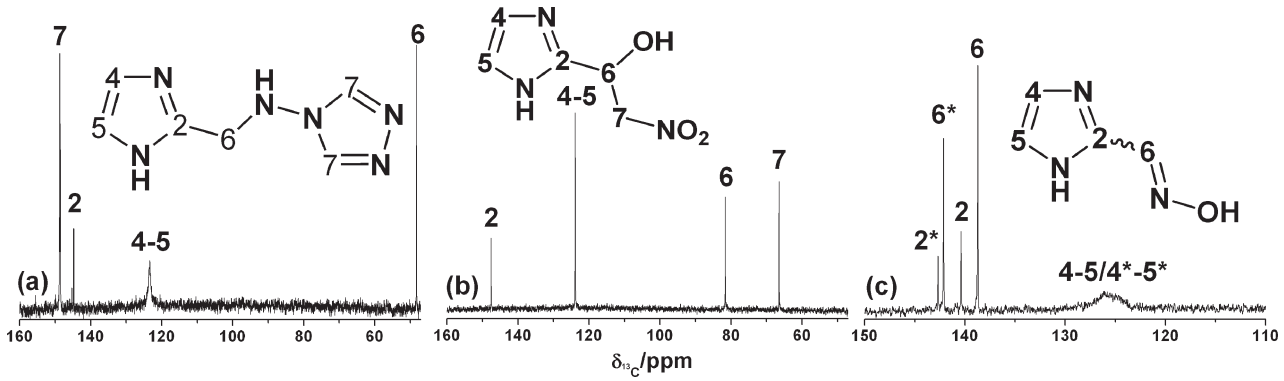


FIGURE 5. ^{13}C NMR spectra of **6** (a), **10** (b), and **8** (c) in DMSO-d_6. The asterisk in the assignment of **8** is for the *syn*- beside the *anti*-isomer.

agreement with **6** and **7**, indicating that the change in the hybridization at C_6 to sp^3 produced the rapid interconversion between the tautomeric forms independent of the characteristics of the solvents.

In addition, according with our 2D NMR studies in the solution state, the conformation of the Schiff bases **5** and **11** was the *E* in both cases (see Supporting Information). However, the presence of the *Z* isomers in rapid equilibrium cannot be excluded.

These results indicate that the formation of a hydrogen bond between the R-NH proton of the imidazole ring and the oxygen or nitrogen of the substituent at C_6 may stabilize the *E* conformation. In addition to this, the geometry optimization performed using DFT at the B3LYP/6-31+G-(2d,p) level using the GAUSSIAN 03 program[19] showed that the distances between the R-NH hydrogen and the nitrogen or oxygen in the imine or aldehyde group, respectively, were right for a hydrogen bond formation in **4**, **5**, **8**, and **11** (the distances were between 2.586 and 2.801 Å). Finally, these results were in full agreement with the calculations, which favored the *E* isomer over the *Z* isomer by 29.60 kJ mol^{-1} in compound **5** and by 22.46 kJ mol^{-1} in **11**, respectively.

Then, there is a lower availability of the R-NH proton for the intermolecular transfer between the 1H and 3H forms, thus reducing the rate of the exchange and generating the existence of two prevalent tautomeric structures in the time of the NMR experiment.[12]

On the other hand, the ^{13}C CP-MAS spectrum of oxime **8** allowed us to resolve the C_{4-5} (Figure 6) in comparison with the ^{13}C NMR spectrum in DMSO-d_6 (Figure 5). In particular the *syn*- and *anti*-isomers were present in the same amounts in the solid state (see NQS data, Figure 6b). Moreover, taking into account the 2D-NMR results of **8** for the

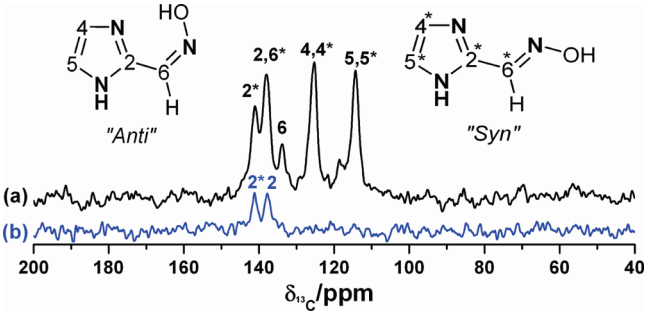


FIGURE 6. ^{13}C CP-MAS (a) and NQS spectra (b) of **8**.

unequivocal assignment of the *syn*/*anti* signals, the ^{1}H spectra in DMSO-d_6 or acetone-d_6 showed that the mixture of *syn*/*anti* was 60:40 in both solvents. Maybe in the liquid state the *syn*-conformation was slightly preferred in relation to the ability of the R-OH group to interact with the solvent.

Finally, we performed variable-temperature NMR studies on **8** (Figure 7). The two well-resolved signals from the protons of the imidazole ring for both the *syn*- and *anti*-isomers and the coalescence of $C_{4-5/4*5*}$ into one signal at 298 K indicated that the proton tautomerism rate was increased in acetone-d_6 in contrast with the results in DMSO-d_6 (Figure 5). It is interesting to see that the ratio between the *syn*- and *anti*-isomers was not affected by the temperature from 298 to 202.3 K, indicating that the isomerization and the tautomeric process were apparently not connected. However, the R-OH and R-NH protons were exchangeable according with our 2D EXSY experiments showing that the tautomeric process may also involve the R-OH protons of the oxime group. Additionally, the ^{13}C spectrum at 202.3 K showed two broad signals for $C_{4,5/4*,5*}$ as in the ^{13}C CP-MAS. Protons of the R-OH from the oxime group for each isomer were assigned according with the HMBC results at 202.3 K (see Supporting Information).

In addition, although the line broadening for the R-NH proton signals is commonly associated with the quadrupolar coupling,[20] in our case the tautomeric process was also involved in that broadening and the resolution in the R-NH proton signals was enhanced with the decrease in

(19) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheesman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishoda, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Otcherski, J.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Danneberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Kamaromi, I.; Martin, L. R.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanaykkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, G.; Pople, J. A. *GAUSSIAN 03, Revison B.03*; Gaussian, Inc.: Pittsburgh, PA, 2003.

(20) Harris, R. K. In *Nuclear Magnetic Resonance Spectroscopy*; Logman Scientific and Technical: London, 1994.

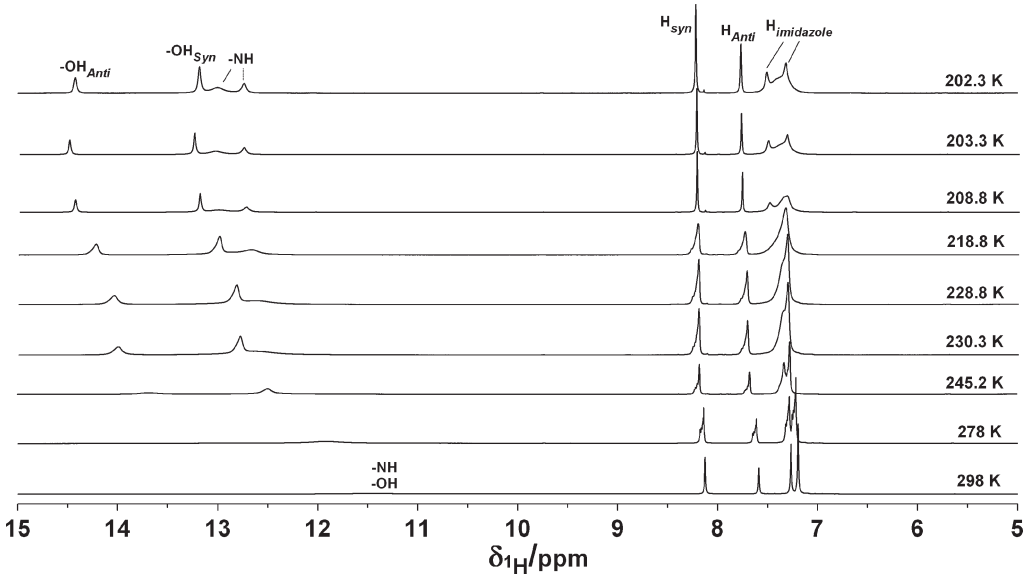


FIGURE 7. Variable-temperature ^{1}H NMR spectra of **8** in acetone-d_6.

temperature to 202.3 K associated with the low proton tautomerism rate (Figure 7).

3. Conclusions

The existence and stability of the hydrate and aldehyde forms of the imidazole-2-carboxaldehyde (**4aq** and **4**) were extensively characterized. We can summarize that the hydrate form **4aq** precipitated from aqueous solution at pH = 8.0 from the solid-state NMR results and that at pH = 6.5 and 9.5 only **4** can be extracted with Cl_2CH_2 in agreement with our FTIR and solid-state NMR experiments. Considering the liquid-state NMR results, hydrate **4aq** was the main species at pH < 6 and the aldehyde **4** the main one at pH > 9. Moreover, the hydrate form evolved to the aldehyde form in methanolic or DMSO solution.

We concluded that the tautomeric process between the 1H and 3H forms was not significantly disturbed by the DMSO-d_6 solvent in compounds **4**, **5**, and **8**. In particular, the oxime **8** in acetone-d_6 showed an increase in the rate of the tautomeric exchange compared to the rate in the DMSO-d_6 solvent. The variable-temperature NMR experiments of **8** indicated that the isomerization and the tautomeric process were apparently not connected.

Finally, we can conclude that the intermolecular association in the time of the NMR scale was affected by the hybridization and the nature of the substitution at C_6. Moreover, the formation of hydrogen bonding between the R-NH proton and the oxygen or the nitrogen of the carbonyl or imine group in **4**, **5** and **11** may be the main cause of the low tautomeric interconversion in the time of the NMR experiment.

4. Experimental Section

4.1. Solid-State NMR Experiments. All solid-state NMR experiments were performed at room temperature in a 300 MHz spectrometer equipped with a 4-mm MAS probe. High-resolution ^{13}C solid-state spectra were recorded using the ramp $\{^1H\}\rightarrow\{^{13}C\}$ CP-MAS. NQS spectra were recorded for compounds **4aq**, **5**, and **8**.[20] Spectral editing with the pulse sequence for cross-polarization with polarization inversion (CPPI) was used in compound **11**.[21] HETCOR spectra in the solid state were recorded for compounds **4**, **4aq**, **5**, and **11** following the sequence presented by van Rossum et al.[22] The contact time for the CP was 200 μs to avoid relayed homonuclear spin-diffusion-type processes. The magic angle pulse length was 2.55 μs. To obtain the ^{1}H spectra, 64 points were collected with a dwell time of 35.5 μs. The acquisition time was 1.14 ms. The spinning rate was 10 kHz for all of the samples and experiments.

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Supporting Information Available: Synthesis and copies of 1D- and 2D-NMR spectra of noncommercially available prepared compounds, FTIR and FTIR-ATR experiments, variable-temperature ^{13}C spectra of **8**, and geometry optimization figures of **5** and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

(21) Wu, X.; Zilm, K. W. *J. Magn. Reson.* **1993**, *102*, 205–213.
(22) van Rossum, B. J.; Förster, H.; de Groot, H. J. M. *J. Magn. Reson.* **1997**, *124*, 516–519.