Spectroscopic analysis of imidazolidines Part V: ^{1}H and ^{13}C NMR spectroscopy and conformational analysis of *N*-acylimidazolidines

María C. Caterina,[a] María V. Corona,[a] Carlos de los Santos,[b] María I. Abasolo,[a] Isabel A. Perillo,[a] and Alejandra Salerno[a]

[a] *Departamento de Química Orgánica, Facultad de Farmacia y Bioquímica, Universidad de Buenos Aires, Junín 956, 1113. Buenos Aires, Argentina*
[b] *Department of Pharmacological Sciences, Stony Brook University-School of Medicine, Stony Brook, NY 11794-8651, USA*
E-mail: asalerno@ffyb.uba.ar

Abstract

The conformational features of a series of 1-acyl-3-arylimidazolidines **1-14** were correlated with their ^{1}H and ^{13}C-NMR spectra. Due to the hindered rotation around the N-CO bond, these compounds exist in solution as a mixture of non-isolable *Z/E* diastereomers, the *Z*- isomer being the most abundant in all cases.

The analysis of NOESY spectra confirmed the complete assignment of the ^{1}H-NMR resonances of each rotamer. Two-dimensional heteronuclear HMQC and HMBC spectra of selected compounds permitted the assignment of ^{13}C-NMR signals. We analyzed the influence of the imidazolidine ring substituents on the equilibrium abundance of *Z/E* isomers. We also studied the spectroscopic and conformational properties of a 1-acyl-2,3-diarylimidazolidine **15**, which revealed the effect of the C-2 substitution.

**Keywords:** Imidazolidines, NMR, hindered rotation, amides, *Z/E* diastereomers, cyclic aminals

Introduction

Tetrahydroimidazoles (imidazolidines) are cyclic aminals of pharmacological interest. Some of these compounds have biological activity, which is strongly dependent on their substitution patterns.[1] In order to elucidate structure-activity correlations, the study of their conformational features, specially the substituent orientation in molecules of biological interest, has been the object of several investigations.

Our laboratory has used ^{1}H- and ^{13}C-NMR spectroscopy to study the conformational characteristics of imidazolidines having different substitution patterns (alkyl or aryl groups) at
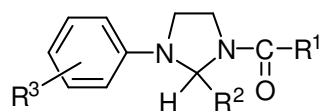
the N-1/N-3 and/or C-2 positions.[2-4] Our previous studies showed that the nitrogen atoms of 1,3-diaryl substituted imidazolidines undergo fast inversion, independent of the presence or absence of C-2 substitution, whereas in the case of 1-alkyl-3-arylimidazolidines fast nitrogen inversion occurs only in the absence of C-2 substitution. In the presence of a C-2 substituent, inversion of the *N*-alkyl nitrogen is slow and the imidazolidine shows a *trans*-like distribution of its *N*-alkyl and C-2 substituents.[2,3]

Electron delocalization originating from the contribution of structure II (Figure 1) gives partial double-bond character to the N-CO amide bond in its ground state, with rotational barriers in the 15-23 kcal/mol range,[5-9] causing the geometric and magnetic non-equivalence of the nitrogen substituents when $R^2 = R^3$ and the presence of diastereomeric amides when $R^2 \neq R^3$.[5-9] In particular, the *E/Z* equilibrium in heterocyclic tertiary amides and related compounds has been reviewed.[10]
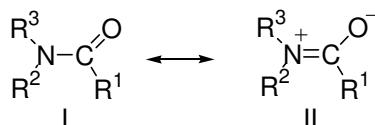
Figure 1. Resonance of amide group.

**Table 1.** 1-Acyl-3-aryl imidazolidines **1-15**

Compound	R^1	R^2	R^3
1	H	H	4-Cl
2	H	H	4-CH$_3$
3	CH$_3$	H	4-CH$_3$
4	CH$_3$	H	4-OCH$_3$
5	C$_2$H$_5$	H	H
6	C$_2$H$_5$	H	4-Cl
7	C$_2$H$_5$	H	3,4-Cl$_2$
8	C$_2$H$_5$	H	4-CH$_3$
9	*iso*-C$_3$H$_7$	H	4-Br
10	*iso*-C$_3$H$_7$	H	4-CH$_3$
11	*iso*-C$_3$H$_7$	H	4-F
12	C$_6$H$_5$	H	4-CH$_3$
13	C$_6$H$_5$	H	4-OCH$_3$
14	4-NO$_2$C$_6$H$_4$	H	4-NO$_2$
15	C$_6$H$_5$	C$_6$H$_5$	4-OCH$_3$

NMR spectroscopic methods have been successfully used for obtaining information about the stereochemistry of amides.[5,6] In line with our previous studies related to spectral and biological properties of imidazolidines,[1-4] we prepared a series of 1-acyl-3-arylimidazolidines[11] (heterocyclic tertiary amides). Because the complete knowledge of structure, including stereochemistry, is essential for lead optimization in drugs discovery, we report herein our studies concerning the structural features of several of those compounds (**1-15**) (Table 1) as studied by NMR spectroscopy. We were particularly interested in determining the influence of the steric and/or electronic effects of the acyl and aryl groups on the conformational features of such compounds as well as the influence of C-2 substitution.

Results and Discussion

N-Acylimidazolidines can undergo three dynamic processes that result from their azacycloalkane character, namely ring reversal, amide rotation and nitrogen inversion.

The room temperature ^{1}H-NMR spectra of the C-2 unsubstituted imidazolidines **1-14** display in all cases two sets of signals that correspond to two different species (Figure 2).
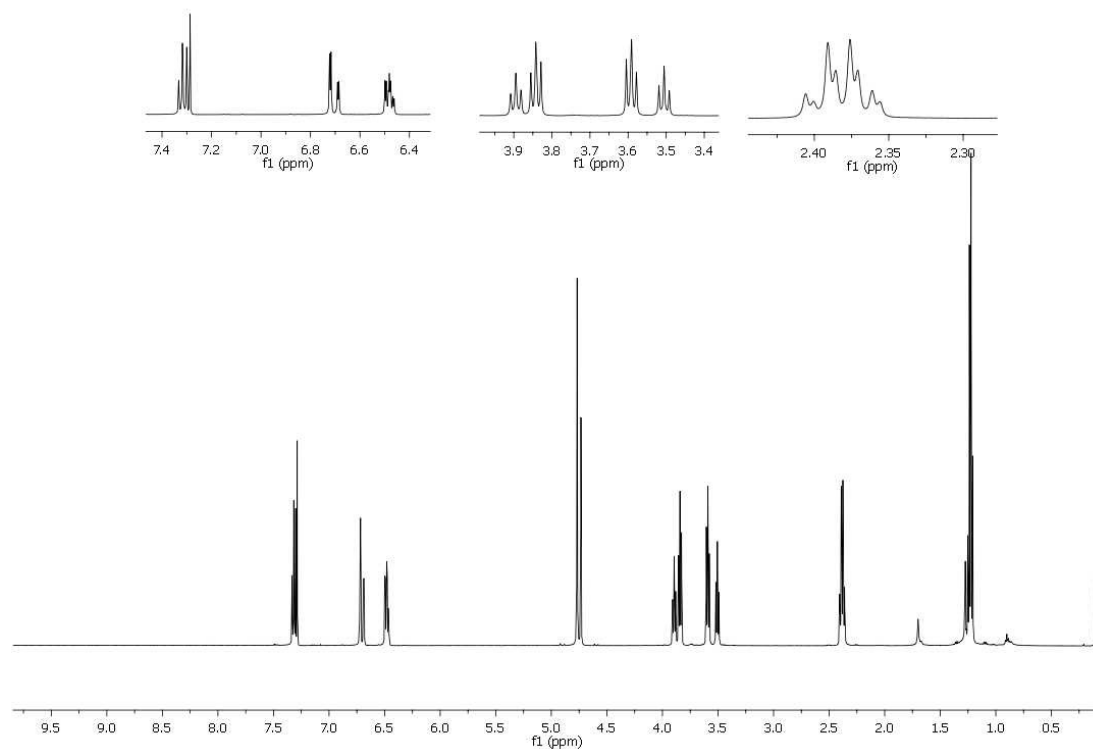
Figure 2. ^{1}H NMR spectrum of compound **7.**

For both forms, the ^{1}H-NMR spectra show isochronicity of C-2, C-4 and C-5 methylene hydrogens of the heterocyclic ring that appear as singlets in the 4.61-5.16 ppm range for H-2 or triplets in the 3.42-3.73 ppm and 3.78-4.18 ppm ranges for H-4 and H-5, respectively (Table 2).

These features are consistent with a fast ring reversal and nitrogen inversion in the NMR time scale at room temperature.[2-4] Therefore, the only observable pr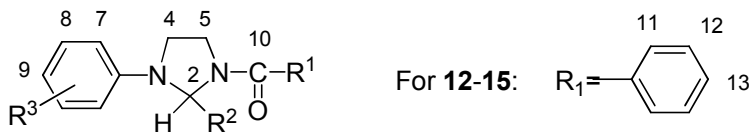ocess is amide rotation and the spectroscopic NMR data suggest the existence in solution of non-isolatable *E/Z* diastereomers that originate from restricted rotation around the N-CO bond (Figure 3).[5-9]
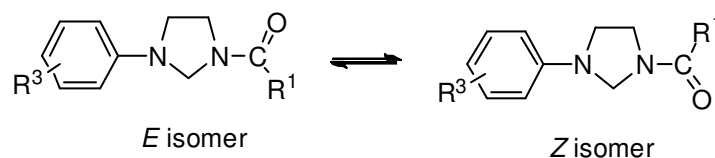
Figure 3. *E/Z* diastereomeric equilibrium in *N*-acilimidazolidines.

Table 2. ^{1}H-NMR signals and relative abundances of imidazolidines **1-15**

Comp. (%)	H-2	H-4	H-5	N-aryl	R[1]
1(*Z*) (54.6)	4.74 (s)	3.51 (t, 6.4)	3.88 (t, 6.4)	7: 6.57 (d, 8.5); 8: 7.07 (d, 8.5)	8.27 (s)
1(*E*) (45.4)	4.78 (s)	3.48 (t, 6.7)	3.83 (t, 6.7)	7: 6.56 (d, 8.7); 8: 7.10 (d, 8.7)	8.38 (s)
2(*Z*) (52.9)	4.75 (s)	3.50 (t, 6.4)	3.88 (t, 6.4)	7: 6.57 (d, 8.6); 8: 7.10 (d, 8.6) CH_3: 2.27 (s)	8.28 (s)
2(*E*) (47.1)	4.78 (s)	3.47 (t, 6.9)	3.82 (t, 6.9)	7: 6.56 (d, 8.6); 8: 7.11 (d, 8.6) CH_3: 2.27 (s)	8.39 (s)
3(*Z*) (57.4)	4.73 (s)	3.54 (t, 6.7)	3.78 (t, 6.7)	7: 6.59 (d, 8.5) ; 8: 7.08 (d, 8.5) CH_3: 2.27 (s)	CH_3: 2.12 (s)
3(*E*) (42.6)	4.70 (s)	3.46 (t, 6.6)	3.78 (t, 6.6)	7: 6.56 (d, 8.2); 8: 7.09 (d, 8.2) CH_3: 2.24 (s)	CH_3: 2.13 (s)
4(*Z*) (57.0)	4.73 (s)	3.57 (t, 6.7)	3.82 (t, 6.7)	7: 6.68 (d, 7.1); 8: 6.87 (d, 7.1) CH_3: 3.78 (s)	CH_3: 2.13 (s)
4(*E*) (43.0)	4.69 (s)	3.46 (t, 6.6)	3.82 (t, 6.6)	7: 6.63 (d, 7.1); 8: 6.89 (d, 7.1) CH_3: 3.79 (s)	CH_3: 2.13 (s)
5(*Z*) (55.2)	4.79 (s)	3.60 (t, 6.7)	3.81 (t, 6.7)	7: 6.67 (t, 8.6); 8: 7.23-7.28 (m) 9: 6.85-6.87 (m)	CH_3: 1.20 (t, 7.4) CH_2: 2.36 (q, 7.4)

Table 2. Continued

| Comp. (%)	H-2	H-4	H-5	N-aryl	R1
5(*E*) (44.8)	4.75 (s)	3.51 (t, 6.7)	3.86 (t, 6.7)	7: 6.67 (t, 8.6); 8: 7.23-7.28 (m); 9: 6.85-6.87 (m)	CH$_3$: 1.21 (t, 7.4) CH$_2$: 2.36 (q, 7.4)
6(*Z*) (59.0)	4.75 (s)	3.56 (t, 6.6)	3.80 (t, 6.6)	7: 6.57 (d, 8.9); 8: 7.20 (d, 8.9)	CH$_3$: 1.19 (t, 7.4) CH$_2$: 2.36 (q, 7.4)
6(*E*) (41.0)	4.71 (s)	3.47 (t, 6.6)	3.85 (t, 6.6)	7: 6.54 (d, 8.9); 8: 7.22 (d, 8.9)	CH$_3$: 1.20 (t, 7.4) CH$_2$: 2.35 (q, 7.4)
7(*Z*) (59.0)	4.74 (s)	3.57 (t, 6.7)	3.82 (t, 6.7)	7: 6.43-6.49 (m); 7´: 6.70 (d, 2.82); 8: 7.25-7.32 (m)	CH$_3$: 1.20 (t, 7.4) CH$_2$: 2.36 (q, 7.4)
7(*E*) (41.0)	4.71 (s)	3.48 (t, 6.8)	3.87 (t, 6.8)	7: 6.43-6.49 (m); 7´:6.67 (d, 2.82); 8: 7.25-7.32 (m)	CH$_3$: 1.22 (t, 7.4) CH$_2$: 2.36 (q, 7.4)
8(*Z*) (55.9)	4.74 (s)	3.54 (t, 6.7)	3.78 (t, 6.7)	7: 6.60 (d, 8.5); 8: 7.09 (d, 8.5); CH$_3$: 2.27 (s)	CH$_3$: 1.20 (t, 7.4) CH$_2$: 2.36 (q, 7.4)
8(*E*) (44.1)	4.70 (s)	3.46 (t, 6.6)	3.84 (t, 6.6)	7: 6.57 (d, 8.3); 8: 7.10 (d, 8.3); CH$_3$: 2.28 (s)	CH$_3$: 1.22 (t, 7.4) CH$_2$: 2.36 (q, 7.4)
9(*Z*) (65.1)	4.74 (s)	3.56 (t, 6.7)	3.83 (t, 6.7)	7: 6.52 (d, 8.6); 8: 7.35 (d, 8.6)	CH$_3$: 1.18 (d, 6.6) CH: 2.70 (h, 6.6)
9(*E*) (34.9)	4.77 (s)	3.47 (t, 6.6)	3.86 (t, 6.6)	7: 6.50 (d, 8.6); 8: 7.37 (d, 8.6)	CH$_3$: 1.19 (d, 6.6) CH: 2.59 (h, 6.6)
10(*Z*) (59.6)	4.74 (s)	3.55 (t, 6.6)	3.84 (t. 6.6)	7: 6.60 (d, 8.5); 8: 7.09 (d, 8.5) CH$_3$: 2.27 (s)	CH$_3$: 1.18 (d, 6.9) CH: 2.70 (h, 6.9)
10(*E*) (40.4)	4.76 (s)	3.46 (t, 6.6)	3.82 (t, 6.6)	7: 6.57 (d, 8.2); 8: 7.11 (d, 8.2); CH$_3$: 2.28 (s)	CH$_3$: 1.189 (d, 6.9) CH: 2.62 (h, 6.9)
11(*Z*) (61.9)	4.73 (s)	3.55 (t, 6.7)	3.85 (t, 6.7)	7: 6.57-6.63 (m); 8: 6.95-7-01 (m)	CH$_3$: 1.18 (d, 6.9) CH: 2.69 (h, 6.9)
11(*E*) (38.1)	4.75 (s)	3.46 (t, 6.7)	3.84 (t, 6.7)	7: 6.57-6.63 (m); 8: 6.95-7-01 (m)	CH$_3$: 1.19 (d, 6.7) CH: 2.60 (h, 6.7)
12(*Z*) (58.2)	4.96 (s)	3.50 (t, 6.6)	3.84 (t, 6.6)	7: 6.66 (d, 7.7); 8: 7.10 (d, 7.7); CH$_3$: 2.27 (s)	11: 7.60 (bs) 12, 13: 7.48 (bs)
12(*E*) (41.8)	4.69 (s)	3.56 (t, 6.6)	4.05 (t, 6.6)	7: 6.51 (d, 7.20); 8: 7.07 (d, 7.20); CH$_3$: 2.28 (s)	11: 7.60 (bs) 12, 13: 7.48 (bs)

Table 2. Continued

Comp. (%)	H-2	H-4	H-5	N-aryl	R1
13(Z) (57.3)	4.91 (s)	3.42 (t, 6.2)	3.82 (t, 6.2)	7: 6.67 (d, 8.7); 8: 6.86 (d, 8.7); CH$_3$: 3.77 (s)	11: 7.56 (bs) 12, 13: 7.44 (bs)
13(E) (43.7)	4.61 (s)	3.48 (t, 6.5)	4.06 (t, 6.5)	7: 6.55 (d, 8.6); 8: 6.81 (d, 8.6) CH$_3$: 3.74 (s)	11: 7.56 (bs) 12, 13: 7.44 (bs)
14(Z) (65.7)	5.16 (s)	3.73 (t, 6.6)	3.95 (bs)	7: 6.58 (bs); 8: 8.16 (bs)	11: 7.76 (dd, 7.2, 2.1) 12: 8.34 (dd, 7.2, 2.1)
14(E) (34.3)	4.82 (s)	3.73 (t, 6.6)	4.18 (bs)	7: 6.49 (bs); 8: 8.16 (bs)	11: 7.76 (dd, 7.2, 2.1) 12:8.34 (dd, 7.2, 2.1)
15 (100.0)	6.59 (s)	3.30-3.50 (m) 3.75-3.85 (m)	3.90-4.00 (m)	7: 6.55 (d, 8.8); 8: 6.77 (d, 8.8); CH$_3$: 3.72 (s)	11: 7.60-7.70 (bs) 12, 13 and R^2: 7.20-7.60 (m)

The assignment of the ^{1}H-NMR signals was performed by analysis of their one-dimensional spectra and confirmed by the correlations observed in the NOESY spectra of selected compounds, **1**, **8** and **12,** as models of *N*-formyl, *N*-alkanoyl and *N*-aroyl derivatives respectively (Figure 4). The remaining compounds of the series were assigned by analogy. In all cases, the abundances of each rotamer were calculated from the intensity of the C-2 methylene signals (Table 2). In all cases, the most abundant isomer corresponds to the *Z* diastereomer that has the R[1] group trans to the C-2 methylene.

The *Z/E* abundance ratio increases with the volume of the R[1] substituent, being smallest in the formyl derivatives **1**, **2** and largest for the isobutyryl compounds **9-11**. Intermediate abundance ratios are found for the *N*-benzoyl derivatives **13** and **14**. The *Z/E* equilibrium is also sensitive to the electronic properties of the substituents in the aryl moiety, R[3], with increased preference for the *Z* diasteromer in the case of electron-withdrawing groups. As an example we can compare the ratio *%Z / %E* for the *N*-phenyl derivative **5** (55.2/44.8) and the *N*-4-chlorophenyl derivative **6** (59/41).

Several conclusions follow the analysis of the ^{1}H-NMR data. The chemical shift of H-2 and H-5 reflects the increased electronegativity of the acyl-substituted nitrogen as compared to with alkyl- or aryl-substituted nitrogens. It has been reported that the H-2 and H-4/H-5 of 1,3-dibenzylimidazolidines resonate around 3.50 and 2.35 ppm, respectively,[3] whereas those of 1,3-

diaryl substituted compounds move downfield, resonating at around 4.60 and 3.55 ppm, respectively,[2] due to electron delocalization through the aniline moiety. In the case of 1-acyl-3-arylimidazolidines **1-14,** the chemical shift of H-2 and H-5 signals around 4.70-5.16 ppm and 3.78-4.18 ppm, respectively, indicates further deshielding, with their value depending on R[1] and the *Z/E* configuration of the compound.
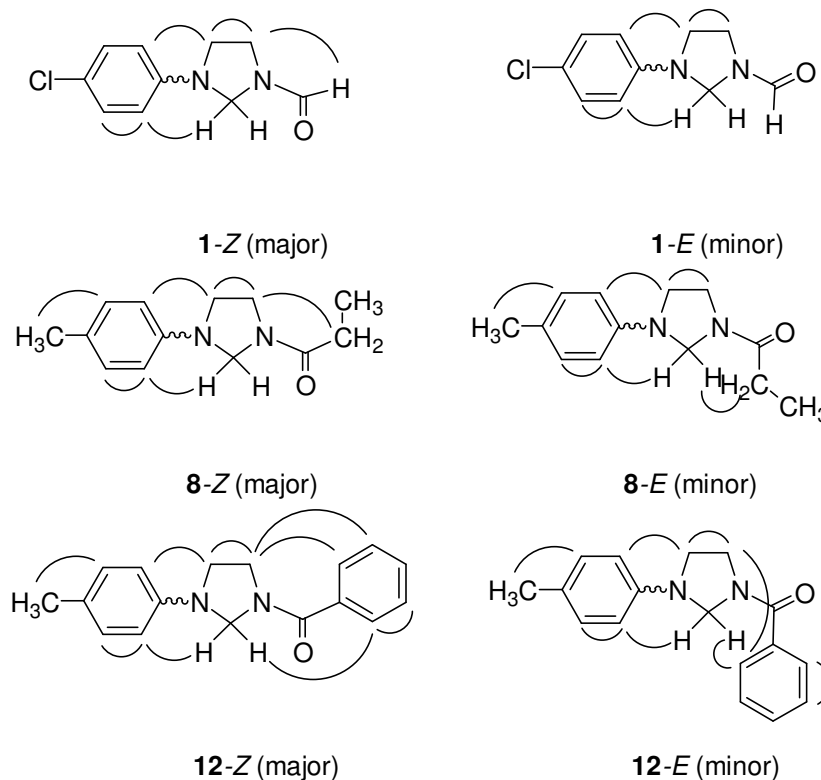

Figure 4. NOESY correlations observed in compounds **1**, **8** and **12**

The chemical shift of the H-2 and H-5 signals in formamides **1** and **2** reflect shielding of hydrogens that are *cis* with respect to the oxygen. Hence, the H-2 chemical shift in the *Z* diastereomer is smaller than in the *E* isomer, whereas the inverse situation occurs at H-5. On the other hand, the phenyl of the benzoyl groups exhibits a larger shielding effect on the adjacent *cis* methylenes than the carbonyl group. Thus, the H-2 signals of the *E* isomers of **12** and **13** resonate around 4.65 ppm, about 0.3 ppm upfield from the values observed for the *Z* diastereomer (around 4.93 ppm). The same effect is observed for the H-5 signals of the same compounds, which resonate approximately 0.2 ppm upfield in the *Z* isomer as compared to the *E* isomer. This correlation is absent for imidazolidines with R[1] = H or alkyl groups, compounds **1** to **11,** which show chemical shift differences smaller than 0.07 ppm for the H-2 and H-5 signals of the diastereomers.

The H-4 signals of compounds **1-14** appear in the 3.42-3.73 ppm range, values that are similar to those previously observed in 1,3-diarylimidazolidines.[2] Chemical shift differences

between the diastereomeric forms are small, being 0.03 ppm for the formyl derivatives **1**-**2**, 0.09-0.11 ppm for the alkyl-substituted compounds **3**-**11** and 0.06 for the *N*-benzoylimidazolidines **12**-**14**.

In all the series, the aromatic proton signals of the *N*-aryl group of both diastereomers appear in general with the expected multiplicity. On the other hand, the benzoyl aromatic hydrogens of both diastereomeric forms of **12** and **13** appear as broad singlets, indicating a low barrier for their interconversion, a fact previously observed for other benzamides.[7] The most likely explanation for this behavior is the competive stabilization between the amide moiety and the phenyl substituent (cross conjugation) which lowers the partial N-CO double bond character (Figure 5).
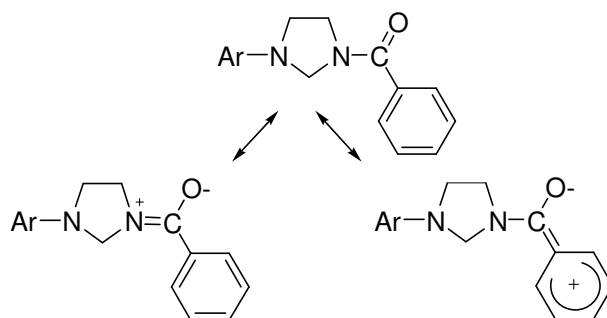
Figure 5. Competitive resonance stabilization between the amide moiety and the benzoyl group.
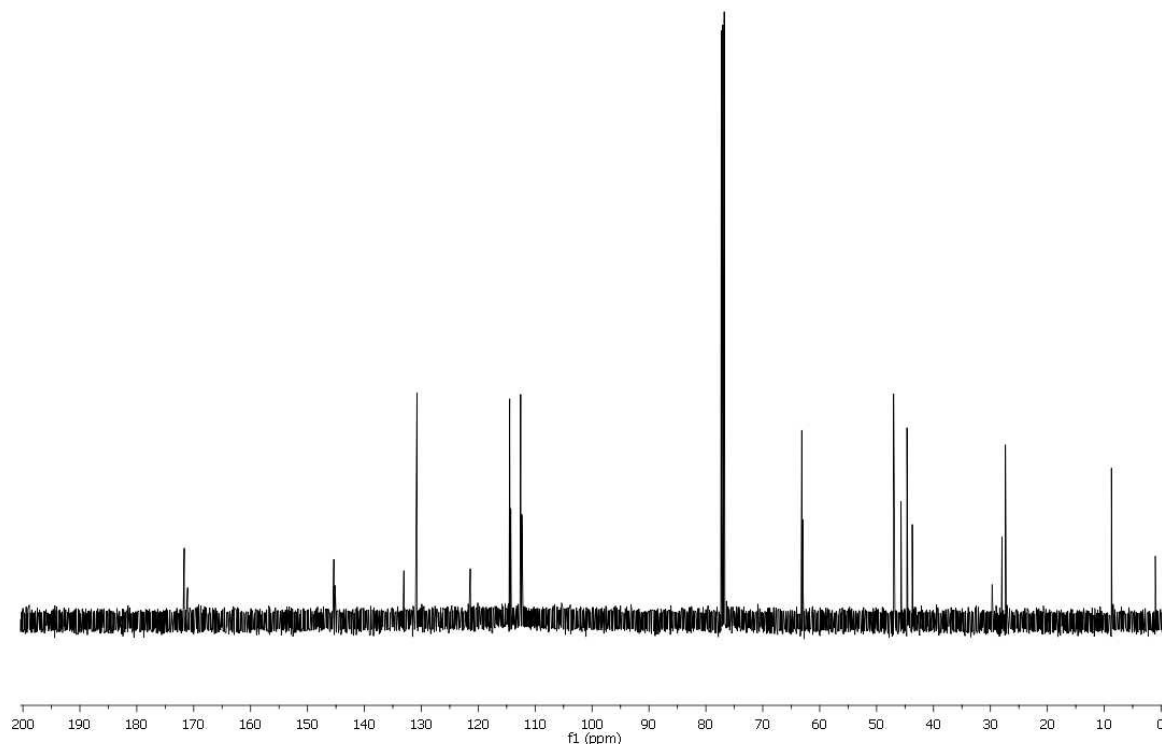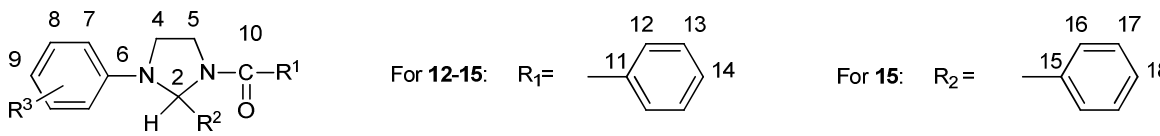

Figure 6. ^{13}C NMR spectrum of compound **7.**

The ^{13}C-NMR spectra of compounds **1-14** also display separate signals for both rotamers. Unambiguous assignment of the ^{13}C resonances followed the analysis of correlations observed in the HMQC and HMBC spectra (Figure 6, Table 3).

Table 3. ^{13}C-NMR signals of imidazolidines **1-15**

For **12-15**: R$_1$= (phenyl, positions 11–14) For **15**: R$_2$ = (phenyl, positions 15–18)

Comp.	C-2	C-4	C-5	C-6	C-7	C-8	C-9	C-10	R^1	R^3
1(*Z*)	61.4	40.0	46.1	144.2	113.1	129.7	131.9	159.9	-	-
1(*E*)	63.1	41.8	44.2	144.2	113.3	129.8	132.2	159.7	-	-
2(*Z*)	61.3	40.0	46.0	144.1	113.4	129.9	128.1	159.7	-	20.0
2(*E*)	62.1	41.5	44.3	144.1	113.2	129.8	128.2	159.6	-	20.0
3(*Z*)	64.1	45.6	48.1	144.1	113.3	127.8	128.0	168.6	21.8	20.2
3(*E*)	64.5	44.1	47.0	144.0	113.4	129.8	128.1	167.7	22.2	20.2
4(*Z*)	64.1	45.8	48.0	140.6			153.0	168.5	21.9	55.6
4(*E*)	64.8	44.0	46.9	140.5			153.1	167.6	22.3	55.6
5(*Z*)	63.4	44.8	47.0	144.3	113.2	129.3	118.6	171.6	CH$_2$: 27.3 CH$_3$: 8.7	-
5(*E*)	63.3	43.8	45.7	144.1	113.0	129.4	118.7	171.2	CH$_2$: 27.9 CH$_3$: 8.8	-
6(*Z*)	63.4	44.7	47.1	144.7	114.3	129.2	123.5	171.6	CH$_2$: 27.3 CH$_3$: 8.7	-
6(*E*)	63.2	43.8	45.8	144.5	114.0	129.3	123.5	171.1	CH$_2$: 27.9 CH$_3$: 8.8	-
7(*Z*)	63.1	44.6	46.9	145.3	7: 112.8, 7´: 114.4	8: 130.7, 8´: 133.1	121.3	171.6	CH$_2$: 27.3 CH$_3$: 8.7	-
7(*E*)	62.8	43.6	45.6	145.1	7: 112.2, 7´: 114.2	8: 130.7, 8´: 133.1	121.3	171.2	CH$_2$: 27.8 CH$_3$: 8.8	-
8(*Z*)	63.7	44.9	47.5	144.2	113.3	129.9	128.0	171.6	CH$_2$: 27.4 CH$_3$: 8.9	20.4
8(*E*)	63.6	43.9	46.1	144.0	113.5	129.9	128.2	171.1	CH$_2$: 27.9 CH$_3$: 9.1	20.4
9(*Z*)	63.4	44.7	47.2	145.1	114.7	132.0	110.7	174.9	CH: 32.0 CH$_3$: 18.8	-
9(*E*)	63.1	43.8	45.6	144.9	114.5	132.1	110.7	174.4	CH: 33.0 CH$_3$: 19.0	-

Table 3. Continued

Comp.	C-2	C-4	C-5	C-6	C-7	C-8	C-9	C-10	R1	R3
10(*Z*)	63.8	44.8	47.5	144.1	113.5	129.8	128.0	174.9	CH: 32.0 CH$_3$: 18.9	20.3
10(*E*)	63.6	44.0	46.0	144.1	113.3	129.9	128.2	174.6	CH: 32.9 CH$_3$: 19.1	20.3
11(*Z*)	64.1	44.8	47.8	142.8	114.3, 114.2	116.0, 115.7	154.9	175.0	CH: 32.0 CH$_3$: 18.8	-
11(*E*)	63.7	44.0	46.3	142.8	114.1, 114.0	116.1, 115.8	154.9	174.1	CH: 33.0 CH$_3$: 19.1	-
12(*Z*)	64.1	47.6	47.7	144.1	113.5	129.9	128.1	169.2	11: 136.1, 12: 126.9, 13, 14: 128.5, 130.6	20.4
12(*E*)	65.8	44.4	46.3	144.1	113.5	129.9	128.2	169.1	11: 137.7, 12: 127.3, 13, 14: 128.5, 130.6	20.4
13(*Z*)	64.6	47.8	48.2	140.8	114.8	130.4	153.0	168.8	11: 135.7, 12: 127.3, 13, 14: 128.4, 128.5	55.6
13(*E*)	66.4	44.5	46.9	140.4	114.8	130.5	153.2	169.0	11: 136.2, 12: 126.9, 13, 14: 128.4, 128.5	55.6
14(*Z*)	63.9	47.4	47.7	144.1	115.8	130.5	132.1	168.7	11: 135.2, 12: 126.6, 13: 127.4, 14: 129.2	
14(*E*)	65.4	44.1	46.7	144.1	115.8	130.5	132.1	169.1	11: 134.5, 12: 126.2, 13: 127.2, 14: 128.5	

Four model compounds, **2**, **8**, **10** and **12**, were investigated computationally, using the conformational analysis module of the SYBYL 8.1 program. The calculated *%Z* values for each

compound are in line with the experimental data measured by integration of ^{1}H NMR signals. Data are reported in Table 4.

Table 4. Abundances of *Z* diastereomer

Compound	experimental data (%)	calculated data (%)
2	52.9	51.00
8	55.9	57.69
10	65.1	60.00
12	57.3	61.27

The 1,2,3-trisubstituted imidazolidine **15** shows a single set of signals in the ^{1}H- and ^{13}C-NMR spectra, indicating the presence of only one diastereomer. The analysis of HMQC and HMBC spectra yielded the complete assignment of ^{13}C-NMR signals that is listed in Table 3.
The H-4, adjacent to the *N*-aryl group, appears as two differentiated multiplets at around 3.30-3.50 ppm and at 3.75-3.85 ppm. In contrast, the H-5 signals are a complex multiplet around 3.90-4.00 ppm. Due to the presence of the phenyl substituent, the H-2 is more deshielded than in compound **13** and appears as a singlet at 6.59 ppm, partially overlapping with the *ortho* hydrogen of the *N*-4-methoxyphenyl group. The *N*-aryl hydrogens of **15** resonate as two resolved doublets at 6.55 and 6.77 ppm, whereas the *N*-benzoyl *ortho* hydrogens are a broad signal at 7.60-7.70 ppm. The other aromatic hydrogens appear as a complex multiplet resonating on the 7.20-7.60 ppm range.

The NOESY spectrum of **15** displays a clear interaction between the *N*-aryl hydrogens (H-7, 6.55 ppm) and both hydrogens of the adjacent methylene group (H-4), indicating that, under our experimental conditions, inversion of the *N*-aryl substituent is fast even in the presence of the C-2 phenyl group. On the other hand, observation of an NOE cross-peak between H-2 (6.69 ppm) and the *ortho* hydrogens of the *N*-benzoyl group (H-11, 7.71 ppm) indicates a short distance among them, suggesting the *E* configuration of the N-CO amide bond, as shown in Figure 7.
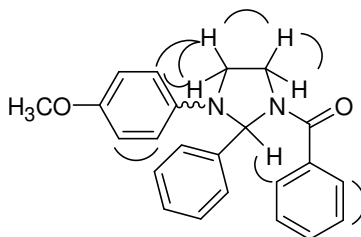
Figure 7. Correlations observed in the NOESY spectrum of compound **15**

Conclusions

We studied the spectroscopic and conformational characteristics of a series of 1-acyl-3-arylimidazolidines at room temperature. Analysis of the NMR data shows that C-2 unsubstituted imidazolidines **1**-**14** exist as an equilibrium mixture of *E/Z* diastereomers, more abundant on their *Z* isomer. In the case of *N*-alkanoyl derivatives **1-11**, preference for the *Z* configuration increases with the size of the acyl group, reflecting the importance of steric hindrance in the *E/Z* equilibrium.

The NMR data also show shielding of the methylene hydrogens adjacent to N-1, specifically H-2 and H-5, by the amide carbonyl and the phenyl of the benzoyl group. At room temperature, the 1,2,3-trisubstituted compound **15** exists as a single diastereomer that, based on NOESY evidence, was later ascribed to the *E* isomer of the N-CO bond.

Experimental Section

General. Reagents, solvents and starting materials were purchased from commercial sources and purified according to standard procedures. Melting points are uncorrected values taken on a Büchi capillary apparatus. One- and two-dimensional ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Avance II 500 spectrometer at room temperature (297.5° K). Standard sample concentrations were 10 mg/mL for ^{1}H- and 25 mg/mL for ^{13}C-NMR, using deuterochloroform as solvent. Chemical shifts (δ) are given in ppm relative to internal TMS and coupling constants are reported in Hz. Splitting multiplicities are reported as singlet (s), broad singlet (bs), doublet (d), triplet (t), quartet (q), heptet (h) and multiplet (m). HMQC, HMBC and NOESY (mixing time, 0.9 seconds) spectra were recorded on a Bruker Avance II 500 spectrometer. Electron ionization mass spectra were recorded with a GC-MS Shimadzu QP-1000 spectrometer operating at 20 eV. TLC analyses were carried out on Silica gel 60 F$_{254}$ using chloroform-methanol (9:1) as solvent.

1-Acyl-3-arylimidazolidines (1-15). These were prepared from the reaction of *N*-acyl-*N´*-arylethylenediamine and the corresponding aldehyde, following literature procedure.[11] The preparation of compounds **3-6, 8, 10** and **12** has been previously described.[11] Melting points, yields and elemental analysis of the new compounds are given below. ^{1}H- and ^{13}C-NMR data are presented in Tables 2 and 3.

3-(4-Chlorophenyl)-1-formylimidazolidine (1). Yield 74%, m.p. 88-89 °C (ethanol). MS (EI): *m/z* (210 M$^{+\cdot}$). Anal. Calcd. for C$_{10}$H$_{11}$ClN$_2$O: C, 57.01; H, 5.26; N, 13.30; found: C, 57.12; H, 5.29; N, 13.20.

1-Formyl-3-(4-methylphenyl)imidazolidine (2). Yield 71%, m.p. 87-88 °C (ethanol). MS (EI): *m/z* (190 M$^{+\cdot}$). Anal. Calcd. for C$_{11}$H$_{14}$N$_2$O: C, 69.45; H, 7.42; N, 14.73; found: C, 69.55; H, 7.32; N, 14.85.

3-(3,4-Dichlorophenyl)-1-propionylimidazolidine (7). Yield 87%, m.p. 106-107 °C (ethanol). MS (EI): *m/z* (272 M$^{+.}$). Anal. Calcd. for $C_{12}H_{14}Cl_2N_2O$: C, 52.76; H, 5.17; N, 10.26; found: C, 52.63; H, 5.20; N, 10.34.

3-(4-Bromophenyl)-1-isobutyrylimidazolidine (9). Yield 88%, m.p. 103-104 °C (ethanol). MS (EI): *m/z* (296 M$^{+.}$). Anal. Calcd. for $C_{13}H_{17}BrN_2O$: C, 52.54; H, 5.77; N, 9.43; found: C, 52.45; H, 5.80; N, 9.35.

3-(4-Fluorophenyl)-1-isobutyrylimidazolidine (11). Yield 88%, m.p. 106-107 °C (ethanol). MS (EI): *m/z* (236 M$^{+.}$). Anal. Calcd. for $C_{13}H_{17}FN_2O$: C, 66.10; H, 7.25; N, 11.86; found: C, 66.26; H, 7.12; N, 11.85.

1-Benzoyl-3-(4-methoxyphenyl)imidazolidine (13). Yield 92%, m.p. 127-128 °C (ethanol). MS (EI): *m/z* (282 M$^{+.}$). Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92; found: C, 72.42; H, 6.31; N, 9.81.

1-(4-Nitrobenzoyl-3-(4-nitrophenyl)imidazolidine (14). Yield 79 %, m.p. 178-181°C (ethanol). MS (EI): *m/z* (342 M$^{+.}$). Anal. Calcd. for $C_{16}H_{14}N_4O_5$: C, 56.14; H, 4.09; N, 16.37; found: C, 56.19; H, 4.17; N, 16.46

1-Benzoyl-3-(4-methoxyphenyl)-2-phenylimidazolidine (15). Yield 85%, m.p. 162-164 °C (ethanol). MS (EI): *m/z* (358 M$^{+.}$). Anal. Calcd. for $C_{23}H_{22}N_2O_2$: C, 77.07; H, 6.19; N, 7.82; found: C, 76.91; H, 6.31; N, 7.70.

Computational Studies. Four model compounds, **2**, **8**, **10** and **12,** were investigated computationally by GRID SEARCH, using the conformational analysis module of the SYBYL 8.1 program,[12] running on a PC-Linux workstation. The optimized conformation of each molecule in the data set was energy minimized employing MMFF94 force field and the Powell conjugate gradient algorithm with a convergence criterion of 0.05 kcal/mol·Å and Gasteiger-Hückel charges.[13,14]The percentage of rotamers, was determined taking 10% of the total generated conformers by the program.

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References

1. Caterina, M. C.; Perillo, I. A.; Boiani, L.; Pezaroglo, H.; Cerecetto, H.; González, M.; Salerno, A. *Bioorg. Med. Chem.* **2008**, *16*, 2226, and references therein.
    http://dx.doi.org/10.1016/j.bmc.2007.11.077

2. Salerno, A.; Buldain, G.; Perillo, I. A. *J. Heterocycl. Chem.* **2001**, *38*, 849.
   http://dx.doi.org/10.1002/jhet.5570380407

3. Perillo, I. A.; de los Santos, C.; Salerno, A. *Heterocycles* **2003**, *6*, 89.
   http://dx.doi.org/10.3987/COM-02-9623

4. Perillo, I. A.; Buldain, G. Y.; Salerno, A. *Heterocycles* **2003**, *60*, 2103.

5. Suárez, C.; Tafazzoli, M.; True, N. S.; Gerrard, S. *J. Phys. Chem.* **1995**, *99*, 8170.
   http://dx.doi.org/10.1021/j100020a045

6. Tafazzoli, M.; Ziyaei-Halimjani, A.; Ghiasi, M.; Fattahi, M.; Saidi, M. R. *J. Mol. Struct.*
   2008, *886*, 24.
   http://dx.doi.org/10.1016/j.molstruc.2007.01.019

7. Stewart, W. E.; Siddall, T.H. *Chem. Rev.* 1**970**, *70*, 517 (and references therein).
   http://dx.doi.org/10.1021/cr60267a001

8. Quintanilla-Licea, R.; Colunga-Valladares, J. F.; Caballero-Quintero, A.; Rodríguez-Padilla,
   C.; Tamez-Guerra, R.; Gómez-Flores, R.; Waksman, N. *Molecules* **2002**, *7*, 662.
   http://dx.doi.org/10.3390/70800662

9. Kim, Y.; Park, Y.-J.; Park, K. K. *J. Mol. Struct.* **2006**, *783*, 61.
   http://dx.doi.org/10.1016/j.molstruc.2005.08.017

10. Kleinpeter, E. *J. Mol. Struct.* **1996**, *380*, 139.
    http://dx.doi.org/10.1016/0022-2860(95)09188-2

11. Caterina, M. C.; Corona, M. V.; Perillo, I.; Salerno, A. *Heterocycles* **2009**, *78*, 771.
    http://dx.doi.org/10.3987/COM-08-11565

12. SYBYL 8.1; Tripos Inc., St. Louis, MO, USA.

13. Clark, M.; Cramer, R. D.; Van Opdenbosch, N. *J. Comput. Chem.* **1998**, *10*, 982.
    http://dx.doi.org/10.1002/jcc.540100804

14. Gasteiger, J.; Marsili, M. *Tetrahedron* **1980**, *36*, 3219.
    http://dx.doi.org/10.1016/0040-4020(80)80168-2