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Synthesis, structural and conformational study of some amides derived from N-methylpiperazine

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Abstract

Some amides (**1**–**6**) derived from *N*-methylpiperazine were synthesized and studied by IR, ^{1}H and ^{13}C NMR spectroscopy. In $CDCl_3$ solution, at room temperature, a fast interconversion of the piperazine ring with the N–CH_3 group in equatorial position can be proposed. α,β-unsaturated compounds **4** and **5** adopt in liquid state and in solution (CCl_4, CCl_2=CCl_2, $CDCl_3$) both *s-cis* and *s-trans* conformations.

Keywords: N-methylpiperazine; Amides; Infrared spectroscopy; NMR spectroscopy; Conformational analysis

1. Introduction

The synthesis of amides derived from piperazine is a subject of interest as several derivatives of this heterocyclic unit have been found to possess important applications in biology [1–3].

As continuation of our studies on the synthesis, spectral properties [4–7] and CoMFA (Comparative Molecular Field Analysis) [8] of heterocyclic compounds with potential therapeutic activity, we report in this paper the synthesis and the structural study using IR and NMR spectroscopies of a series of amides derived from *N*-methylpiperazine (Scheme 1). The unambiguous assignment of all proton and carbon resonances was achieved through the application of one dimensional selective NOE (Nuclear Overhauser Effects), two dimensional NMR techniques-homonuclear NOESY and heteronuclear ^{1}H–^{13}C gHSQC (gradient Heteronuclear Single Quantum Correlations) correlated spectroscopy—and DR (double resonance) experiments. The existence of *s-cis* and *s-trans* conformations of α,β,-unsaturated compounds (**4**, **5**) has been determined with the aid of NOE in NMR and solvent effects on the IR carbonyl band.

2. Experimental

NMR spectra were recorded in $CDCl_3$ on a Varian UNITY-5OOFT spectrometer (499.843 MHz for ^{1}H and 125 MHz for ^{13}C). The standard vendor supplied gHSQC pulse sequences were used. The double resonance experiments involved the use of conventional irradiation, and were performed on a Varian Mercury spectrometer (299.949 MHz).

The IR spectra of compounds **1**–**6** were recorded on a Perkin–Elmer FTIR 1725X spectrophotometer, assisted by a computer, between KBr windows in the 4000–400 cm^{-1} region and in $CDCl_3$ solution (~0.15 M) in the 4000–900 cm^{-1} region using 0.2 mm NaCl cells. Spectra of compounds **4** and **5** were also registered in CCl_4 and CCl_2=CCl_2 solution at various concentrations. The reported wavenumbers are estimated to be accurate to within ±3 cm^{-1}.

2.1. Synthesis

The synthesis of compounds **1**–**6** is summarized in Scheme 1.

A solution of 1-methylpiperazine (10 mmol) in dry tetrahydrofurane (10 mL) was added to a stirred mixture of the corresponding acyl chloride (10 mmol) and triethylamine in tetrahydrofurane (10 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature with continued stirring for 2–5 h. Filtration and removal of solvent under reduced

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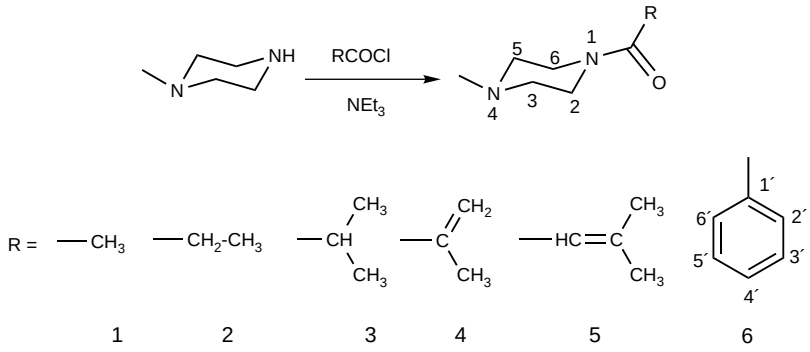

Scheme 1. Synthesis of amides **1**–**6**.

pressure afforded a yellow oil that was purified by treatment with diethyl ether.

3. Results and discussion

3.1. NMR spectra

3.1.1. Spectral analysis and assignment

The ^{1}H NMR spectra of compounds **1**, **2**, **3**, **5** and **6** show great similarity being slightly different the spectrum of compound **4**.

The assignment of proton and carbon resonances for compounds **1**–**6** was made on the basis of DR, NOE, NOESY and gHSQC experiments. The values of the ^{1}H NMR chemical shifts were deduced by analysis of the respective spin systems. These values with the signal assignments are listed in Table 1. The ^{13}C data are tabulated in Table 2.

In the ^{1}H NMR spectra of compounds **1**, **2**, **3**, **5** and **6** the signals corresponding to the piperazine moiety appear as a singlet at 2.17–2.27 ppm, two partially overlapped multiplets at 2.21–2.32 ppm and 2.24–2.42 ppm and two multiplets at 3.50–3.75 ppm and 3.31–3.52 ppm. The ^{1}H NMR spectrum of compound **4** is similar to those of compounds **1** ,**2**, **3**, **5** and **6** except for the multiplets at 3.50–3.75 ppm and 3.31–3.52 ppm where overlapping resonances, centered at 3.52 ppm, were observed.

The singlet at 2.17–2.27 ppm has been assigned to the *N*–CH_3 protons in all compounds.

For the assignment of the signals corresponding to the C2, C6, C3 and C5 protons, NOE and DR experiments for compound **3** have been performed.

Saturation of the proton of the isopropyl group showed NOE enhancements in the two signals, which appear at low field (3.41 and 3.51 ppm) (Fig. 1). Taking into account the gHSQC data (Fig. 2), these signals correspond to protons of two different carbons (C6 and C2 protons). Taking also into account the anisotropic and the steric effects exerted by the amide group, the signal at lower field (3.51 ppm) has been assigned to H2ax(H2eq) and the signal at higher field (3.41 ppm) to H6ax(H6eq).

The multiplets centered at 2.30 and 2.34 ppm are assigned to the C3 and C5 protons. Double resonance experiments have been used to clarify the assignments of the signals corresponding to these protons. By irradiation of the H2ax(H2eq) signal (3.51 ppm), the multiplet at 2.30 simplifies to a singlet and,

Table 1
^{1}H NMR chemical shifts (δ, ppm) and multiplicities for compounds **1**–**6**, in $CDCl_3$

δ (ppm)[a]	**1**	**2**	**3**	**4**		**5**		**6**
				s-cis	*s-trans*	*s-cis*	*s-trans*	
H2ax(H2eq) (m)	3.50	3.52	3.51	[b]	3.52	3.57	3.62	3.75
H6ax(H6eq) (m)	3.31	3.38	3.41	[b]	3.52	3.41	3.32	3.39
H3ax(H3eq) (m)	2.21	2.30	2.30	[b]	2.32	2.26	2.26	2.30
H5ax(H5eq) (m)	2.24	2.30	2.34	[b]	2.32	2.30	2.30	2.42
N–CH_3 (s)	2.17	2.20	2.18	[b]	2.25	2.20	2.19	2.27
$COCH_3$	1.94 (s)	–	–	–	–	–	–	–
CH_2CH_3	–	2.20 (m)	–	–	–	–	–	–
CH_2CH_3	–	1.02 (t)	–	–	–	–	–	–
$CH(CH_3)_2$	–	–	2.66 (m)	–	–	–	–	–
$CH(CH_3)_2$	–	–	0.99 (d)	–	–	–	–	–
CH_3–C=CH_2	–	–	–	[b]	1.88 (s)	–	–	–
CH_3–C=CH_2	–	–	–	[b]	5.12 (s), 4.96 (s)[c]	–	–	–
CH=$C(CH_3)_2$	–	–	–	–	–	1.78 (d), 1.73 (d)[d]	2.07 (d), 1.80 (d)[d]	–
CH=$C(CH_3)_2$	–	–	–	–	–	5.67 (s)	6.13 (s)	–
Ph	–	–	–	–	–	–	–	7.35 (m)

[a] Abbreviations: d, doublet; m, multiplet; t, triplet; s, singlet.
[b] Not determined due to the low resolution of the signals.
[c] H in *cis* disposition with respect to the CH_3 group.
[d] CH_3 in *cis* disposition with respect to the vinyl proton.

Table 2
^{13}C NMR chemical shifts (δ, ppm) for compounds **1–6**, in $CDCl_3$

	1	**2**	**3**	**4**		**5**		**6**
				s-cis	*s-trans*	*s-cis*	*s-trans*	
C5	56.21	54.71	55.09	53.34[a]	53.95[b]	54.99	55.15	55.07
C3	54.40	54.33	54.54	53.67[a]	53.80[b]	54.60	54.46	55.07
C6	45.26	44.81	45.01	45.00	45.75	41.19	40.93	47.25
C2	40.89	40.99	41.26	42.06	40.18	25.76	27.68	41.69
N–*C*H$_3$	46.52	45.60	45.77	44.78	44.88	45.85	46.18	45.69
*C*O	168.63	172.78	174.87	169.00	169.83	166.95	167.57	170.16
CO*C*H$_3$	29.89	–	–	–	–	–	–	–
*C*H$_2$CH$_3$	–	26.25	–	–	–	–	–	–
CH$_2$*C*H$_3$	–	9.35	–	–	–	–	–	–
*C*H(CH$_3$)$_2$	–	–	29.79	–	–	–	–	–
CH(*C*H$_3$)$_2$	–	–	19.28	–		–	–	–
*C*H$_3$–C=CH$_2$	–	–	–	17.11	19.47	–	–	–
CH$_3$–C=*C*H$_2$	–	–	–	104.17	114.12	–	–	–
CH$_3$–*C*=CH$_2$	–	–	–	133.84	139.54	–	–	–
CH=C(*C*H$_3$)$_2$	–	–	–	–	–	19.99	23.34, 21.35	–
*C*H=C(CH$_3$)$_2$	–	–	–	–	–	118.89	123.43	–
CH=*C*(CH$_3$)$_2$	–	–	–	–	–	145.13	145.72	–
C1′	–	–	–	–	–	–	–	135.66
C2′(6′)	–	–	–	–	–	–	–	128.32
C3′(5′)	–	–	–	–		–	–	126.89
C4′	–	–	–	–	–	–	–	129.53

[a,b] These values may be interchanged.

therefore, this signal can be assigned to H3ax(H3eq). Moreover, saturation of the signal corresponding to H6ax(H6eq) (3.41 ppm) simplifies the signal at 2.34 ppm; therefore, this signal must correspond to H5ax(H5eq). It can be noted that the spectrum of compound **3** shows only a signal for H2ax and H2eq, H6ax and H6eq, H3ax and H3eq and H5ax and H5eq as can be deduced by gHSQC data, what has also been observed for compounds **1**, **2**, **4–6**. This fact suggests a conformational dynamics of the piperazine ring, which is fast enough on the NMR time-scale to give one average signal. To assess this suggestion ^1H NMR at −50 °C for compound **4** has been performed, no significative changes having been observed.

Bearing in mind the similarity of the ^1H NMR spectra for the amide **3** and the other amides (**1**, **2**, **4–6**), the complete and unambiguous assignment of the individual protons for the piperazine system of amides **1–6** has been made (Table 1).

For the assignment of ^{13}C NMR chemical shifts (Table 2), substituent and electronic effects were taken into consideration. Once the resonances of the respective protons were established, the analysis of the gHSQC spectrum of **3** allowed the interpretation of the chemical shifts values of the different carbons of compounds **1–6**.

3.1.2. Conformational study

We used ^1H and ^{13}C NMR techniques along with one dimensional selective NOE, NOESY and variable temperature experiments, to analyse the conformations of compounds **1–6** and the following general features were deduced:

a. In $CDCl_3$ solution, at room temperature, a fast interconversion of the piperazine ring with an equatorial position of the N–CH_3 group can be proposed.
b. A restricted rotation around the N–CO bond is deduced.
c. The α,β-unsaturated amides **4** and **5** exist in two nearly planar *s-cis* and *s-trans* conformations.

These conclusions are supported by the following experimental data:

–The N–CH_3 ^1H chemical shifts of compounds **1–6** of 2.17–2.27 ppm have the same values as those found in equatorial N–CH_3 substituted piperazines [9] and related compounds [10–12]. Moreover, selective NOESY as well as selective irradiation of the N–CH_3 group for compound **4** show exclusively correlations with H3 and H5 but not with H2 and H6. In the case of an axially standing methyl group, NOEs between the protons of the methyl group and H2ax, H6ax should occur.

–The N–CH_3 ^{13}C chemical shifts of compounds **1–6** of 44.78–46.52 ppm are in agreement with previously reported values in related compounds with an equatorial disposition of this group [10–12].

As said before, the presence of one signal for the axial and equatorial protons of the piperazine ring suggests a

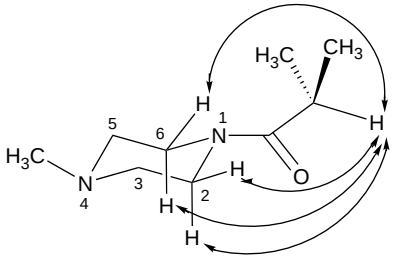

Fig. 1. NOE enhancements in compound **3**.

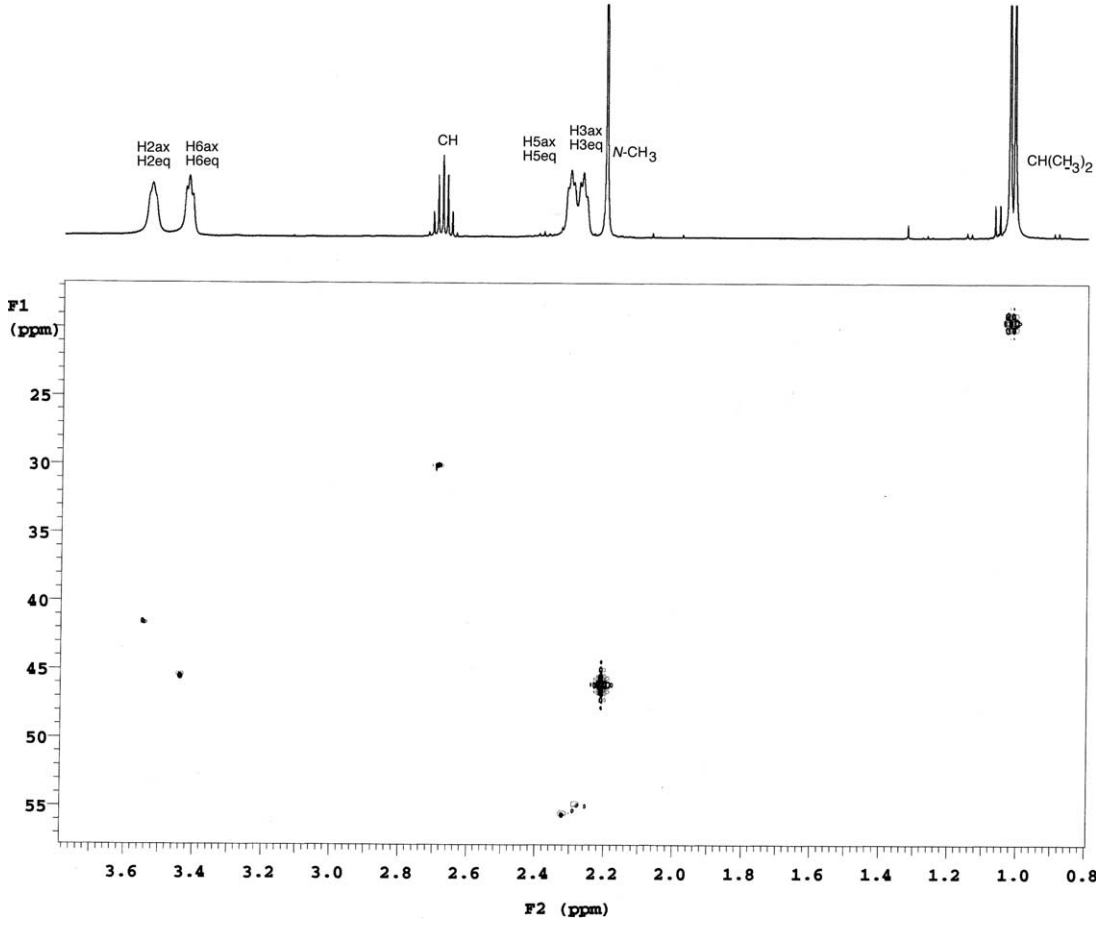

Fig. 2. gHSQC spectrum of compound **3**.

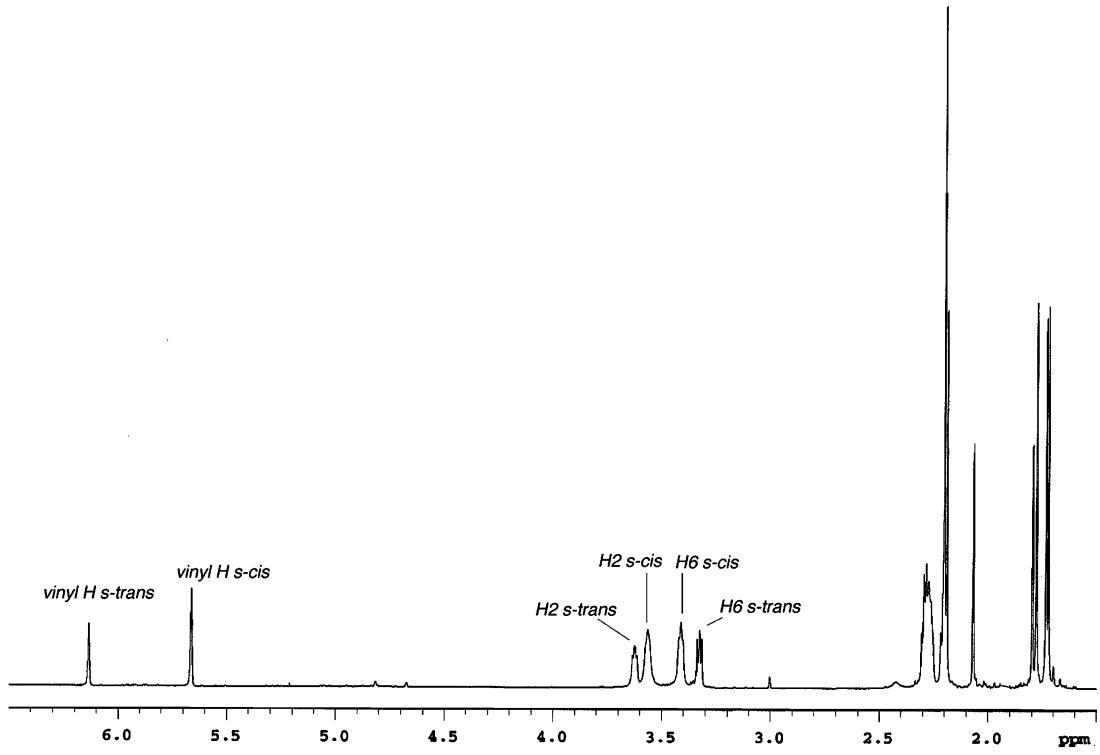

Fig. 3. ^{1}H NMR spectrum of compound **5**.

conformational dynamics for the piperazine ring [9]. Temperature dependent experiments for compound **4** support this hypothesis. When the temperature was lowered at −50 °C, the resolution of the signals in the ^{1}H NMR spectrum does not increase, suggesting a fast exchange regime between conformations.

–The non-equivalence of the C2 and C6 protons and also of the C2 and C6 accounts for a restricted rotation around the N–CO amide bond.

–The α,β,-unsaturated amides **4** and **5** can adopt in solution two nearly planar *s-cis* and *s-trans* conformations. The ^{1}H NMR spectrum of **5** in $CDCl_3$ at room temperature contains two sets of signals (Fig. 3); consequently, these duplicity can be attributed to the presence of the two conformations differing in their arrangement around the C=C bonds.

The signals corresponding to the *s-cis* and *s-trans* conformations have been assigned by NOE experiments (Table 1). We may expect an observable NOE for the vinyl proton in the amide **5** with the *s-cis* conformation but not with the *s-trans* (Fig. 4). Experimentally, the signal at 5.67 ppm (vinyl proton) shows NOE with the signals at 3.57, 3.41 and 1.73 ppm, and therefore these signals correspond to the *s-cis* conformation. The signal at 3.57 ppm has been assigned to H2ax and H2eq, the signal at 3.41 ppm to H6ax and H6eq, and finally, the signal at 1.73 ppm to the CH_3 group, in a *cis* disposition with respect to the vinyl proton. The signal at 1.78 ppm must correspond to the CH_3 group, in a *trans* disposition.

The signal at 6.13 ppm only shows NOE with the signal at 1.80 ppm; therefore these signals correspond, respectively, to the vinyl proton and the CH_3 group in a relative *cis* position, of the *s-trans* conformation. The signal at 2.07 ppm is assigned to the CH_3 group in a *trans* disposition with respect to the vinyl proton.

The signals at 2.26 and 2.30 ppm corresponding to H3ax(H3eq) and H5ax(H5eq), respectively, for both *s-cis* and *s-trans* conformations, appear partially overlapped.

In our working conditions and taking into account the relative proportions of the ^{1}H NMR signals for both *s-cis* and *s-trans* conformations, we can deduce that both conformers are present in the amounts of 61% (*s-cis*) and 39% (*s-trans*).

The ^{13}C NMR spectrum of compound **5** also shows two sets of signals (Table 2). These results are in agreement with the existence of both *s-cis* and *s-trans* conformers.

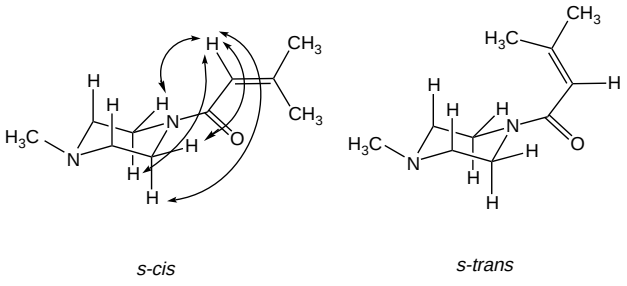

Fig. 4. *s-cis* and *s-trans* conformations of compound **5**. NOE effects for the vinyl proton in the *s-cis* conformation.

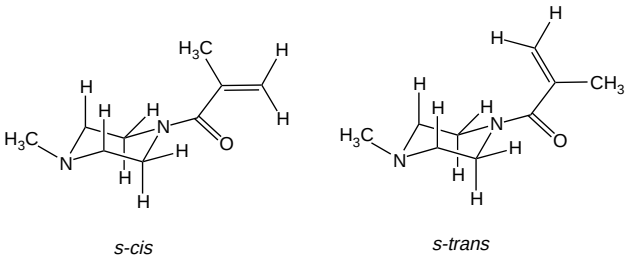

Fig. 5. *s-cis* and *s-trans* conformations of compound **4**.

In the case of the α-CH_3 substituted amide **4**, the presence of the *s-cis* and *s-trans* conformations (Fig. 5) cannot be deduced from the ^{1}H NMR spectrum due to the broadening of the signals. However, the ^{13}C NMR data in $CDCl_3$ solution for this compound show the existence of both conformations being the *s-trans* (the most sterically favoured) the preferred conformation (*s-cis*/*s-trans* = 10:90).

3.2. IR spectra

According to the literature [13] the carbonyl stretching frequencies of the *N*,*N*-dialkylsubstituted amides are a little lower than those of the monosubstituted amides. IR and NMR studies on the conformation of α,β-unsaturated *N*,*N*-dimethyl amides have shown the existence of nearly planar *s-cis* and *s-trans* conformations [14]. The *s-cis* conjugated compounds have normally markedly higher frequencies than the *s-trans*.

The tertiary amides **1**–**6** are characterized by the presence of a very strong band in the 1623–1644 cm^{-1} region in the 'liquid' state and at 1614–1635 cm^{-1} in $CDCl_3$ solution, assigned to the carbonyl group (νC=O). The low frequencies of the CO bands indicate a strong amide bond, so a restricted rotation of the O=C–R residue can be assumed. These results are in agreement with the NMR conclusions.

The amides **1**–**3** with an alkyl group show the νC=O band at 1635–1644 cm^{-1} in liquid state and at 1625–1635 cm^{-1} in $CDCl_3$ solution. As expected, compound **6** absorbs at lower frequency (1632 cm^{-1} in liquid state, and 1622 cm^{-1} in $CDCl_3$) than **1**–**3** as a result of conjugation of the carbonyl group with the aromatic nucleus. Moreover, in this case the characteristic aromatic bands of a monosubstituted aromatic ring are present in the spectrum (i.e. 3000–3100; 1470–1605 cm^{-1}, etc.).

As it could be anticipated, in the case of the α,β,-unsaturated compounds **4**, **5** the carbonyl frequency varies with the conformation (nearly planar *s-cis* or *s-trans*). The infrared spectra of compound **4** show a strong band at 1623 cm^{-1} in the liquid state and at 1617 cm^{-1} in $CDCl_3$ solution, which is assigned to the carbonyl band of the nearly planar *s-trans* form. In both cases, a weaker band (shoulder) at higher frequency (about 1645 cm^{-1}) is attributed to the *s-cis* conformation. The relative intensity of this band increases in carbon tetrachloride solution (1649 cm^{-1}) and even more in tetrachloroethylene solution (1653 cm^{-1}). Consequently, the relative intensity of the *s-trans* band decreases. Moreover, the frequency of this band (1617 cm^{-1} in $CDCl_3$) is shifted to 1628 (CCl_4) or

1630 cm^{-1} (CCl_2=CCl_2), respectively, what can also be attributed to a solvent effect.

These results suggest the existence of equilibrium between the *s-cis* and the *s-trans* conformers, the proportion of the latter increasing in the liquid and in $CDCl_3$ solution.

The ν(C=C) bands could not be detected in the infrared spectra, probably due to overlapping by the strong ν(C=O) bands.

Finally, a weak band at 3062–3066 cm^{-1} is assigned to the CH_2= group (*anti*symmetric stretch).

The infrared spectrum of compound **5** shows a strong band at 1626 cm^{-1} in the liquid state which is shifted to 1615 cm^{-1} in $CDCl_3$ solution, and as in compound **4** is assigned to a twisted *s-trans* conformation. A shoulder at higher frequencies (about 1665 cm^{-1}) is attributed to the presence of a *s-cis* form. Contrary to results in **4**, the spectra in this region do not change much in CCl_4 or in CCl_2=CCl_2 solution except for the increasing of the *s-trans* carbonyl frequencies (1634 or 1639 cm^{-1}, respectively).

4. Conclusions

Six amides derived from 1-methylpiperazine (**1**–**6**) have been synthesized and their conformational preferences studied.

The ^{1}H NMR spectra of the amides show only one signal for axial and equatorial protons of the piperazine ring suggesting an interconversion of this ring between conformations. Besides, a preference of the N–CH_3 group for an equatorial position can be deduced.

NMR and IR data reveal that in $CDCl_3$ (and other solvents) solution the α,β-unsaturated amides **4** and **5** exist as equilibrium mixtures of *s-cis* and *s-trans* conformations.

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