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E/*Z* equilibrium in tertiary amides – Part 3: *N*-acyl-*N*′-arylhexahydro-1,3-diazepines

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HIGHLIGHTS

- We present the NMR spectral characterization of *N*-acyl-*N*′-arylhexahydrodiazepines **1**.
- Compounds **1** display *E*/*Z* isomerism and display two sets of signals.
- Differential assignment was made by analysis of ASIS effects, NOESY and HSQC spectra.
- The influence of both *N*-substituents and ring size on the *E*/*Z* equilibrium is analyzed.
- This is the first stereochemical study on *N*-acylhexahydrodiazepines in the literature.

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ABSTRACT

The ^{1}H and ^{13}C NMR spectroscopic study of a series of *N*-acyl-*N*′-arylhexahydro-1,3-diazepines **1** is presented. Due to hindered rotation around the (O)C–N bond, tertiary amides **1** exist as a mixture of non separable *E*/*Z* diastereoisomers, which show separate signals in their NMR spectra. For some selected derivatives, differential assignment of the ^{1}H resonances of the *E*/*Z* rotamers was made on the basis of the magnitude of ASIS (anisotropic solvent induced shifts) effects and confirmed by NOESY. The corresponding ^{13}C signals were unambiguously attributed by HSQC experiments. The influence of steric and electronic features of the substituents on the relative populations of *E*/*Z* rotamers is analyzed. The effect of the ring size was also investigated by comparison with the corresponding hexahydropyrimidine homologs.

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1. Introduction

Cyclic aminals are compounds of interest due to their pharmacological and chemical properties. The five and six membered heterocyclic aminals (imidazolidines and hexahydropyrimidines, respectively) are found in many bioactive compounds, like anti-inflammatory and analgesic agents, fungicides, antibacterials, parasiticides and antivirals [1–4]. They also behave as prodrugs of pharmacologically active di [5] and polyamines [6] and as protecting groups in the selective functionalization of such compounds. Although imidazolidines and hexahydropyrimidines have received a great deal of attention, their higher homologs (hexahydro-1,3-diazepines) have been less studied, maybe due to the intrinsical difficulty of ring closure reactions leading to seven-membered cyclic aminals [7]. In previous work, we developed a method for the synthesis of *N*-acyl-*N*′-arylhexahydro-1,3-diazepines **1** using microwave irradiation [8]. A limitation of such procedure is that the reaction does not tolerate bulky substituents in either the aryl or the acyl moieties.

Structural features of amides have been widely studied by NMR spectroscopy and molecular modeling, as they represent model compounds for the peptide bond [9]. In particular, the *E*/*Z* equilibrium in heterocyclic tertiary amides and related compounds has been reviewed [10]. The planar arrangement of the substituents in amides, due to partial (O)C–N double bond character, has a strong influence on the superstructure of peptides and proteins [11], while *E*/*Z* isomerization is a key process involved in protein folding and biocatalysis [12].

The partial double bond character of the (O)C–N linkage in amides causes a substantial rotational barrier, which ranges between 15 and 23 kcal/mol [13,14]. For unsymmetrically *N*-substituted amides, hindered rotation entails the existence of non isolable *E*/*Z* diastereoisomers. In the NMR spectra, the rotamers can be observed as two different sets of signals unless the equilibrium is highly biased towards one of them.

In previous work we investigated the *E*/*Z* equilibrium in tertiary amides derived from the hexahydropyrimidine core [15]. The absence of literature data on *N*-acyl derivatives of the homologous

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seven membered cyclic aminals (hexahydrodiazepines) led us to investigate the *E/Z* equilibrium in compounds **1** employing NMR spectroscopy, as part of ongoing research on nitrogen derivatives with hindered rotation [15–22]. The compounds under study are of interest as synthetic analogs of the natural polyamine putrescine.

2. Experimental

2.1. Chemistry

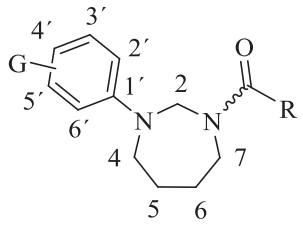
Compounds **1a–h** were prepared by condensation of the corresponding *N*-acyl-*N*′-aryl-1,4-butanediamines [23] and excess aqueous formaldehyde under microwave irradiation [8], and purified by column chromatography.

Yields and analytical data for new compounds **1d,f** are as follows:

1-Formyl-3-phenyl hexahydrodiazepine **1d** was obtained as an oil (73%). MS (EI), *m/z* 204. IR *v*: 3060.44, 2924.22, 2853.25, 1667.67, 1598.01, 1359.82, 970.58, 751.18, 693.19 cm^{-1}, among others. Anal Calcd. for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.89; N, 13.71, found C, 70.49; H, 7.94; N, 13.69.

1-Acetyl-3-(4-bromophenyl)hexahydrodiazepine **1f** was obtained as off-white needles (60%), Mp 95–96 °C (dichloromethane/hexane). MS (EI), *m/z* 296 and 298. IR *v*: 2917.65, 2849.52, 1634.81, 1589.71, 1412.64, 1249.92, 1177.09, 810.37, 500.89 cm^{-1}, among others. Anal. Calcd. for $C_{13}H_{17}BrN_2O$: C, 52.54; H: 5.77; N: 9.43, found: C, 52.61; H: 5.73; N: 9.40.

Table 1
N-Acyl-*N*′-arylhexahydrodiazepines **1a-h**.



Compound **1**	G	R
a	4-Cl	H
b	4-Cl	CH_3
c	4-Cl	C_2H_5
d	H	H
e	H	CH_3
f	4-Br	CH_3
g	4-Cl	C_6H_5
h	4-CH_3	C_6H_5

2.2. Spectra

^1H, ^{13}C NMR, HSQC, and phase-sensitive NOESY spectra were recorded on a Bruker Avance II 500 MHz spectrometer. Spectra were acquired from samples as solutions at room temperature in 5 mm tubes. Unless otherwise indicated, deuterochloroform was used as the solvent. The standard concentration of the samples was 10 and 40 mg/mL for ^1H and ^{13}C NMR, respectively. Chemical shifts are reported in ppm (δ) relative to TMS as an internal standard. Coupling constants are reported in Hz. Multiplicities are quoted as singlet (s), doublet (d), triplet (t), double triplet (dt), triple triplet (tt), quartet (q), multiplet (m) and broad signal (bs). IR spectra were run in a Perkin Elmer Spectrum one FT-IR spectrometer.

3. Results and discussion

The compounds described in this work are shown in Table 1. ^1H NMR chemical shifts and multiplicities of *E/Z* diastereoisomers of

Table 2
^1H NMR signals of compounds **1a-h** ($CDCl_3$).

Cpd	**2**	**7**	**4**	**5**, **6**	Aromatics	R	G
1a (*Z*)	5.06 (s)	3.23–3.25 (m)	3.61–3.63 (m)	1.74–1.89 (m)*	2′,6′: 6.71 (d, 9.2) 3′,5′: 7.19–7.22 (m)	8.23 (s)	–
1a (*E*)	4.90 (s)	3.42–3.44 (m)	3.50–3.52 (m)		2′,6′: 6.67 (d, 9.2) 3′,5′: 7.19–7.22 (m)	8.28 (s)	–
1b (*Z*)	5.13 (s)	3.26–3.30 (m)	3.56–3.58 (m)	1.78–1.94 (m)	2′,6′: 6.70 (d, 9.1) 3′,5′: 7.19 (d, 9.1)	2.14 (s)	–
1b (*E*)	4.93 (s)	3.50–3.54 (m)*		1.50 (bs)	2′,6′: 6.65 (d, 9.2) 3′,5′: 7.21 (d, 9.2)	2.15 (s)	–
1c (*Z*)	5.14 (s)	3.28–3.30 (m)	3.54–3.56 (m)	1.75–1.83 (m)	2′,6′: 6.69 (d, 9.1) 3′,5′: 7.17 (d, 9.1)	CH_3: 1.16 (t, 7.3) CH_2: 2.36 (q, 7.3)	–
1c (*E*)	4.92 (s)	3.49–3.52 (m)*		1.66–1.74 (m)	2′,6′: 6.64 (d, 8.9) 3′,5′: 7.20 (d, 8.9)	CH_3: 1.19 (t, 7.3) CH_2: 2.35 (q, 7.3)	–
1d (*Z*)	5.09 (s)	3.23–3.25 (m)	3.64–3.66 (m)	1.73–1.77 (m), 1.85–1.89 (m)	2′,4′,6′: 6.75–6.83 (m) 3′,5′:7.24–7.28 (m)*	8.24 (s)	–
1d (*E*)	4.93 (s)	3.43–3.45 (m)	3.53–3.55 (m)	1.80–1.83 (m)	2′,4′,6′: 6.73–6.79 (m) 3′,5′:7.24–7.28 (m)*	8.30 (s)	–
1e (*Z*)	5.16 (s)	3.29–3.31 (m)	3.60–3.62 (m)	1.77–1.85 (m)	2′,4′,6′: 6.74–6.79 (m) 3′,5′: 7.24–7.29 (m)*	2.14 (s)	–
1e (*E*)	4.97 (s)	3.52–3.54 (m)	3.55–3.57 (m)	1.72–1.76 (m)	2′,4′,6′: 6.79–6.83 (m) 3′,5′: 7.24–7.29 (m)*	2.16 (s)	–
1f (*Z*)	5.10 (s)	3.26–3.28 (m)	3.52–3.54 (m)	1.71–1.80 (m)*	2′,6′: 6.63 (d, 9.2) 3′,5′: 7.30 (d, 9.2)	2.10 (s)	–
1f (*E*)	4.90 (s)	3.47–3.49 (m)*			2′,6′: 6.58 (d, 9.1) 3′,5′: 7.32 (d, 9.1)	2.12 (s)	-
1g (*Z*)	5.32 (s)	3.23–3.25 (m)	3.65–3.67 (m)	1.80–1.84 (m), 1.70–1.74 (m)	2′,6′: 6.78 (d, 8.9) 3′,5′: 7.24 (d, 8.9)	7.36–7.43 (m)	–
1g (*E*)	4.94 (s)	3.53 (bs)	3.61 (bs)	1.93 (bs), 1.87 (bs)	2′,6′: 6.43 (d, 8.9) 3′,5′: 7.12 (d, 8.9)	7.45–7.53 (m)	–
1h (*Z*)	5.30 (s)	3.21–3.23 (m)	3.65–3.67 (m)	1.76–1.81 (m), 1.64–1.69 (m)	2′,6′: 6.75 (d, 8.2) 3′,5′: 7.09 (d, 8.2)	7.37 (bs)	2.27 (s)
1h (*E*)	4.91 (s)	3.52 (bs)	3.59 (bs)	1.84 (bs), 1.88 (bs)	2′,6′: 6.43 (d, 8.2)3′,5′: 6.98 (d, 8.2)	7.44 (m)	2.22 (s)

* Overlapping signals.

Table 3
^{1}H NMR signals of compounds **1a,b,e,g** (C_6D_6).

Cpd.	**2**	**7**	**4**	**5**	**6**	Aromatics	R
1a (*Z*)	4.68 (s)	2.30–2.32 (m)	2.74–2.77 (m)	1.00–1.05 (m)	0.85–0.89 (m)	2′,6′: 6.39 (dd, 9.16, 3.43) 3′,5′: 7.09–7.11 (m)*	7.82 (s)
1a (*E*)	3.82 (s)	3.04–3.06 (m)	2.65–2.68 (m)	1.05–1.09 (m)	1.15–1.19 (m)	2′,6′: 6.08 (dd, 9.16, 3.43) 3′,5′: 7.09–7.11 (m)*	7.83 (s)
1b (*Z*)	4.88 (s)	2.48–2.50 (m)	2.78–2.80 (m)	1.08–1.13 (m)	0.96–1.00 (m)	2′,6′: 6.46 (dd, 9.16, 3.43) 3′,5′: 7.11–7.14 (m)	1.67 (s)
1b (*E*)	4.01 (s)	3.22–3.24 (m)	2.73–2.75 (m)	1.29–1.33 (m)	1.36 (bs)	2′,6′: 6.11 (dd, 9.16, 3.43) 3′,5′: 7.11–7.14 (m)	1.65 (s)
1e (*Z*)	5.17 (s)	2.69–2.71 (m)	3.09–3.11 (m)	1.27–1.36 (m)*	1.13–1.17 (m)	2′,4′,6′: 6.84–6.87 (m) 3′,5′: 7.29–7.32 (m)*	1.82 (s)
1e (*E*)	4.33 (s)	3.42–3.44 (m)	3.04–3.06 (m)	1.27–1.36 (m)*	1.44–1.46 (m)	2′,6′: 6.11 (d, 7.68) 3′,5′: 7.29–7.32 (m)* 4′: 6.90 (tt, 7.10, 1.14)	1.83 (s)
1g (*Z*)	5.21 (s)	2.91 (bs)	2.96 (bs)*	1.21 (bs)	1.08 (bs)	2′,6′: 6.61 (bs) 3,5′: 7.44 (bs)*	7.15–7.25 (m)*
1g (*E*)	4.46 (bs)	3.51 (bs)	2.95 (bs)*	1.53 (bs)	0.78 (bs)	2′,6′: 6.16 (bs) 3′,5′: 7.44 (bs)*	7.15–7.25 (m)*

* Partially overlapping signals.

Table 4
^{13}C NMR signals of compounds **1a-h** ($CDCl_3$).

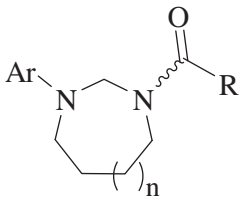
Cpd.	2	7	4	5, 6	1′	2′,6′	3′,5′	4′	R	C = O	G
1a (*Z*)	60.07	46.54	50.92	25.49, 28.01	144.61	113.82	129.47	122.94	–	162.34	–
1a (*E*)	63.62	42.97	49.65	25.47, 27.18	145.34	114.22	129.42	ND	–	161.73	–
1b (*Z*)	61.08	46.72	50.49	26.04, 27.49	144.80	113.69	129.36	122.41	22.36	170.62	–
1b (*E*)	64.62	43.84	50.04	26.07, 27.24	145.57	113.96	129.40	122.90	22.52	169.62	–
1c (*Z*)	61.27	45.66	50.46	26.06, 27.26	144.90	113.72	129.33	122.32	27.54, 9.40	173.80	–
1c (*E*)	63.72	43.94	49.99	26.03, 27.33	145.61	113.89	129.37	122.32	27.46, 9.27	172.85	–
1d (*Z*)	60.19	46.35	50.78	25.64, 28,21	145.84	112.48	129.61	117.95	–	162.29	–
1d (*E*)	63.51	42.86	49.46	25.51, 27.29	146.01	113.00	129.53	118.24	–	161.83	–
1e (*Z*)	61.29	46.46	50.34	25.97, 27.78	146.20	112.42	129.60	117.55	22.41	170.52	–
1e (*E*)	64.59	43.66	49.95	26.18, 27.30	146.21	112.82	129.57	118.06	22.49	ND	–
1f (*Z*)	60.95	46.67	50.38	25.96, 27.42	145.19	114.16	132.22	109.54	22.30	170.57	–
1f (*E*)	64.48	43.82	49.87	25.98, 27.17	ND	114.38	132.24	109.97	22.46	ND	–
1 g (*Z*)	62.16	48.35	51.13	26.03, 27.54	144.67	113.60	129.72	122.68	1″: 131.44 2″,6″: 126.84 3″,5″: 128.46 4″: 129.48	171.54	–
1 g (*E*)	65.50	44.89	50.18	25.96, 26.75	145.03	113.71	129.73	123.14	1″: 131.46 2″,6″: 127.22 3″,5″: 128.52 4″: 129.22	169.45	–
1 h (*Z*)	62.59	48.08	50.93	26.06, 27.91	143.73	112.32	130.24	129.97	1″: 136.83 2″,6″: 126.84 3″,5″: 128.39 4″: 129.53	171.40	20.23
1 h (*E*)	65.74	44.65	50.27	26.15, 26.96	143.69	112.67	129.93	129.88	1″: 136.98 2″,6″: 127.19 3″,5″: 128.49 4″: 129.70	ND	14.18

compounds **1a–h** ($CDCl_3$) are given in Table 2. ^{1}H NMR chemical shifts and multiplicities of compounds **1a,b,e,g** in C_6D_6 are shown in Table 3. ^{13}C NMR chemical shifts of compounds **1a–h** ($CDCl_3$) are given in Table 4. Relative populations of *E/Z* rotamers of compounds **1** and of the corresponding hexahydropyrimidine derivatives **2** ($CDCl_3$) [15] are listed in Table 5.

As mentioned before, unsymmetrically *N,N*-disubstituted amides display *E/Z* stereoisomerism due to restricted rotation around the (O)C–N bond. Consequently, their NMR spectra usually show two sets of signals. As expected, two unequally populated sets of signals are present in the spectrum of **1a**, corresponding to *E/Z* diastereoisomers (Fig. 1). Ring inversion in compounds **1** is expected to be a fast process in the NMR timescale at room temperature, resulting in dynamic averaging of both hydrogens within each methylene group. This is in accordance with the number of signals observed in the ^{1}H NMR spectra of hexahydrodiazepines **1**.

Like many other compounds, amides display the so called ASIS (anisotropic solvent induced shifts) effect [24]. Signals of *N*-alkyl groups *trans* to the carbonyl oxygen experience a stronger diamagnetic shift ($\Delta\delta$) on changing the solvent from $CDCl_3$ to C_6D_6 than their *cis* counterparts [13]. This effect can be diagnostic for the differential assignment of *cis* and *trans N*-substituents. In our experience, it is more reliable than assignment based on chemical shifts in model compounds, especially for amides containing additional anisotropic substituents [20]. Fig. 2 shows, as an example, the differential ASIS effect experienced by the N–CH_2 signals of compound **1a**. Following the afore mentioned criterion for this compound, the singlet corresponding to CH_2 (2) of the major diastereoisomer (δ = 5.06 ppm) was attributed to the *cis N*-methylene, and the one corresponding to the minor species (δ = 4.90 ppm) as *trans* to the carbonyl oxygen ($\Delta\delta$ = 0.38 and 1.08 ppm, respectively, Fig. 2). Signals centered at 3.62 and 3.24 ppm were tentatively

Table 5
E/*Z* ratios for compounds **1a–h** (*n* = 1) and their six membered ring homologs **2** (*n* = 0) [15]



Compound **1**,**2**	Ar	R	*E*:*Z* (*n* = 1)	*E*:*Z* (*n* = 0)
a	4-ClC_6H_4	H	29:71	39:61
b	4-ClC_6H_4	CH_3	20:80	28:72
c	4-ClC_6H_4	CH_2CH_3	20:80	26:74
d	C_6H_5	H	33:67	48:52
e	C_6H_5	CH_3	25:75	37:63
f	4-BrC_6H_4	CH_3	20:80	ND
g	4-ClC_6H_4	C_6H_5	26:74	41:59
h	4-$CH_3C_6H_4$	C_6H_5	31:69	ND

assigned to positions 4 and 7 of the major diastereoisomer. The signal centered at 3.24 ppm (major diastereoisomer) shows a stronger diamagnetic shift ($\Delta\delta$ = 0.93 ppm) than the one at 3.43 ppm (minor diastereoisomer, $\Delta\delta$ = 0.38 ppm), indicating that the former is *trans* to the carbonyl oxygen. As expected, the diamagnetic shifts experienced by the signals corresponding to CH_2 (4) are very similar for both rotamers, while signals arising from CH_2 (7) show very different $\Delta\delta$ depending on their situation with respect to the carbonyl group.

The remaining signals were attributed to the major and minor species on the basis of their relative integration. This assignment was confirmed in the NOESY spectrum of **1a** (Fig. 3), which also confirmed the assignment of positions 4 and 7 of both species. The existence of NOe between signals belonging to the *N*-aryl and the formyl proton in the *Z* rotamer shows that in the averaged conformation of the heterocycle both substituents are in a cisoid relationship, in which the *N*-aryl is not coplanar with the heterocyclic ring.

The ^{13}C spectrum of **1a** also displays separate signals for both rotamers around the (O)C–N bond. Unambiguous differential assignment of the resonances (Table 4) was performed on the basis of the correlations observed in the HSQC spectrum.

Relative populations of *E*/*Z* rotamers of **1a** (Table 5) were determined by integration of well resolved resonances in the ^1H NMR spectrum ($CDCl_3$). ^1H and ^{13}C NMR signals of formamide **1d** were assigned by analogy with **1a**.

In order to assess the influence of the amide substituent R on the spectral features and *E*/*Z* ratio of compounds **1**, some 3-(4-chlorophenyl) substituted 1-acyl derivatives were analyzed. ^1H NMR spectra of amides **1b,c** all display two unequally populated sets of signals. Resonances of amide *N*-methylenes (positions 2 and 7) of **1b** were assigned on the basis of their $\Delta\delta$ (Tables 2 and 3): for the major diastereoisomer, the singlet at 5.13 ppm was attributed as *cis*, while the one at 4.93 ppm (minor rotamer) as *trans* to the carbonyl oxygen ($\Delta\delta$ 0.25 and 0.92 ppm, respectively). Conversely, the upfield multiplet centered at 3.28 ppm was assigned as *trans* (major diastereoisomer, $\Delta\delta$ 0.79 ppm) and the signal centered at and 3.52 ppm as *cis* (minor diastereoisomer, $\Delta\delta$ 0.29 ppm) *N*-methylenes. The remaining signals were attributed to the major and minor species on the basis of their relative integration. This assignment was confirmed by the correlations observed in the NOESY spectrum of **1b** (Fig. 3). ^1H NMR spectra of propionamide **1c** and acetamides **1e,f** were assigned by analogy. The *E*/*Z* ratios determined for compounds **1a-f** (Table 5) shows, in all cases, a preference for the *Z* rotamer.

At variance with the previous examples, in the ^1H and ^{13}C NMR spectra of benzoyl derivatives **1g,h** the signals of both species show line broadening, indicative of a comparatively lower barrier for the interconversion of the *E*/*Z* diastereoisomers. This feature was previously observed in other benzamides, and is attributed to competitive resonance stabilization between the amide moiety and the phenyl substituent, which lowers the partial (O)C–N double bond character [13]. Interestingly, line broadening is more pronounced in the minor rotamer, as shown in Fig. 4 for **1g**. It has to be taken into account that *E*/*Z* interconversion is a unique process that would involve both diastereoisomers. The observed difference could indicate that a dynamic process different from *E*/*Z* interconversion, probably ring inversion, is comparatively slower in the NMR timescale for this rotamer at room temperature. However, it cannot be excluded that this efffect could arise from differences in $\Delta\delta$ for both rotamers. Analysis of the NOESY spectrum of **1g** (Fig. 3) shows that, also in this case, the *Z* rotamer is the major species.

For compounds **1b,g**, unambiguous differential assignment of the ^{13}C resonances of both rotamers (Table 3) was performed on the basis of the correlations observed in their HSQC spectra.

Analysis of data reported in Table 5 shows that the *Z* rotamer is the most stable species in compounds **1**. It can also be observed that this preference is influenced by the nature of both *N*-substituents. In

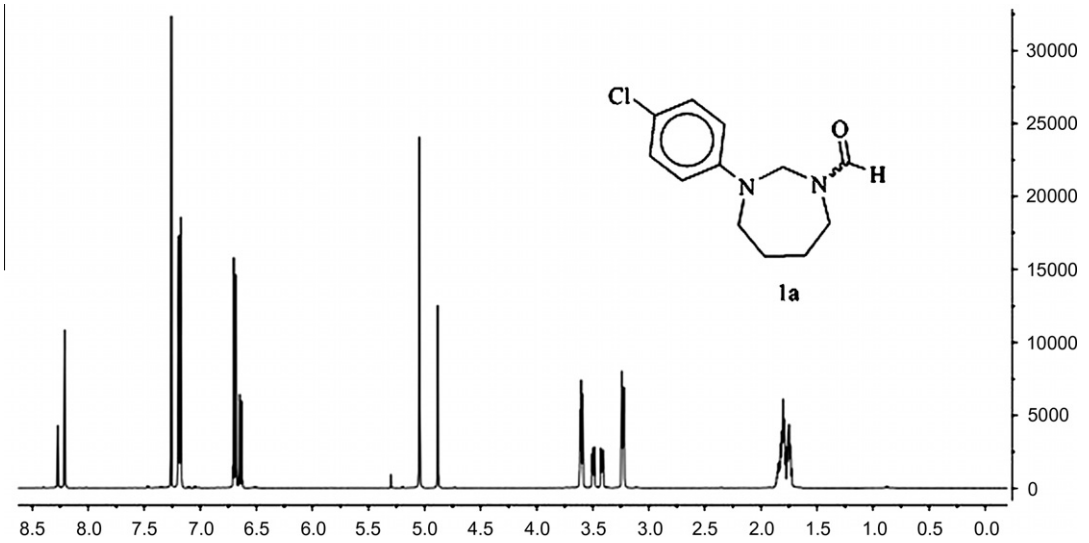


Fig. 1. ^1HNMR spectrum of **1a** ($CDCl_3$).

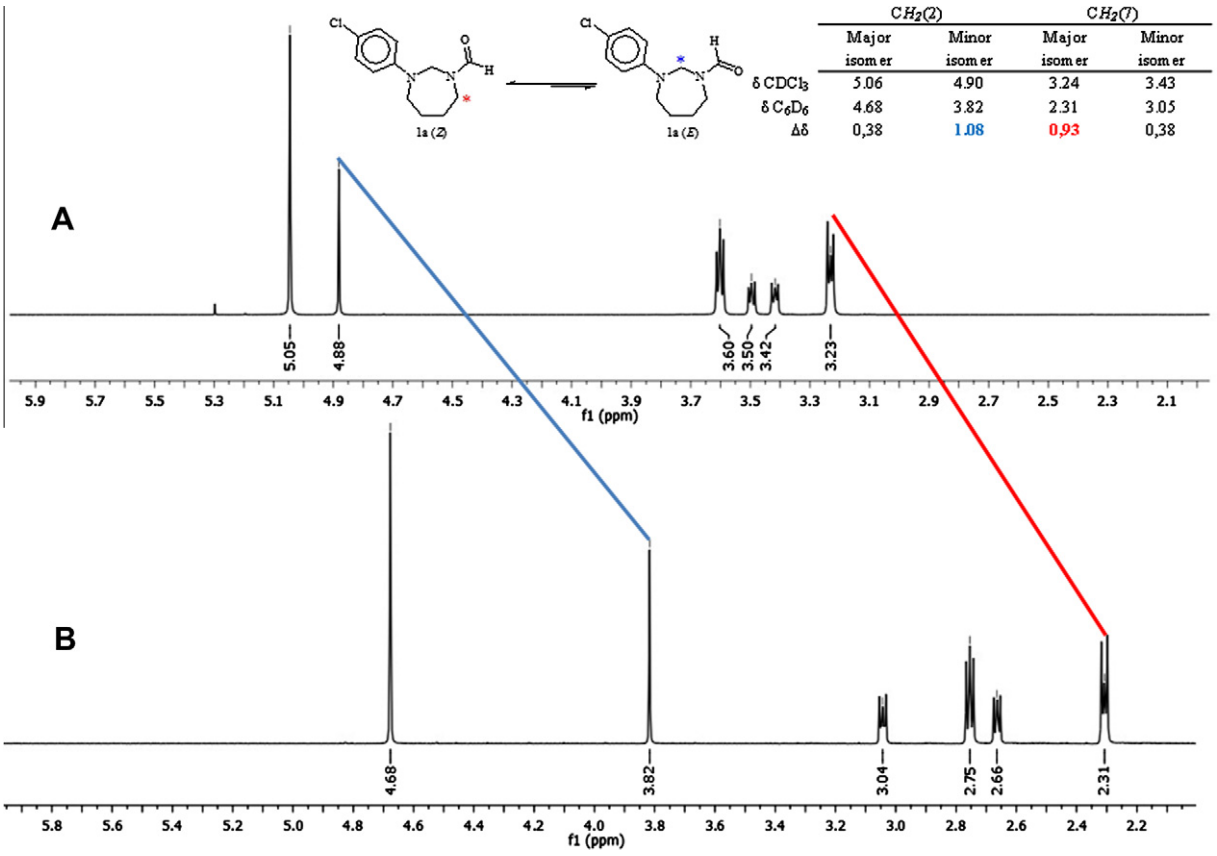


Fig. 2. Detail of the ^{1}HNMR spectra of **1a** in $CDCl_3$ (A) and C_6D_6 (B). In the formulae, ∗ indicates the signal experiencing the strongest ASIS for each rotamer.

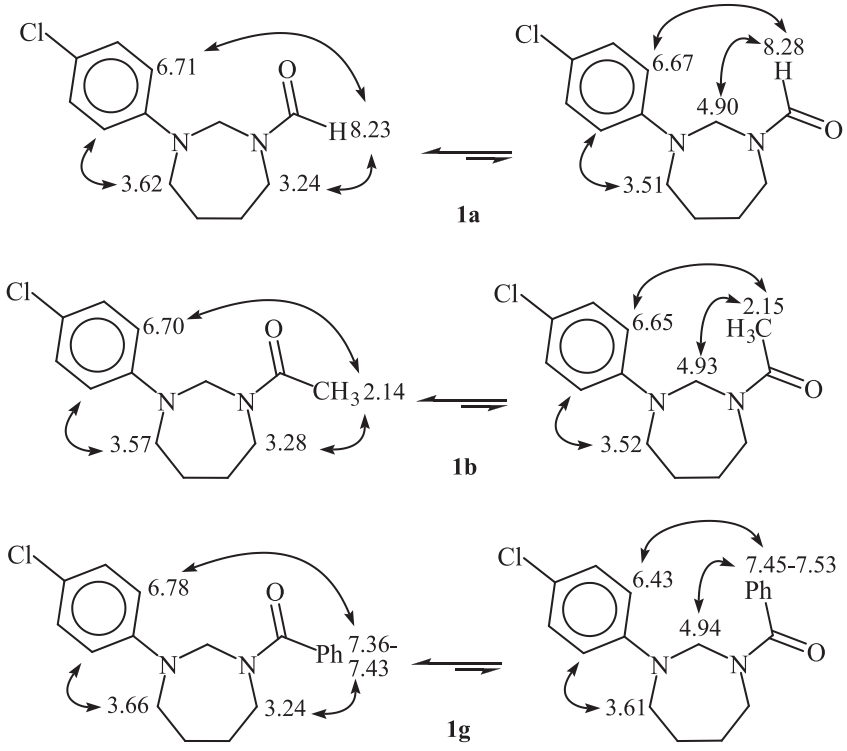


Fig. 3. Relevant NOESY correlations for **1a,b,g**.

the series of 3-(4-chlorophenyl)-1-acyl hexahydrodiazepines **1a–c**, replacement of R = H (**1a**) by CH_3 (**1b**) in the acyl group significantly enhances the *Z* preference. The equilibrium distribution is not further affected when replacing R = CH_3 by C_2H_5 (**1c**). It is noteworthy

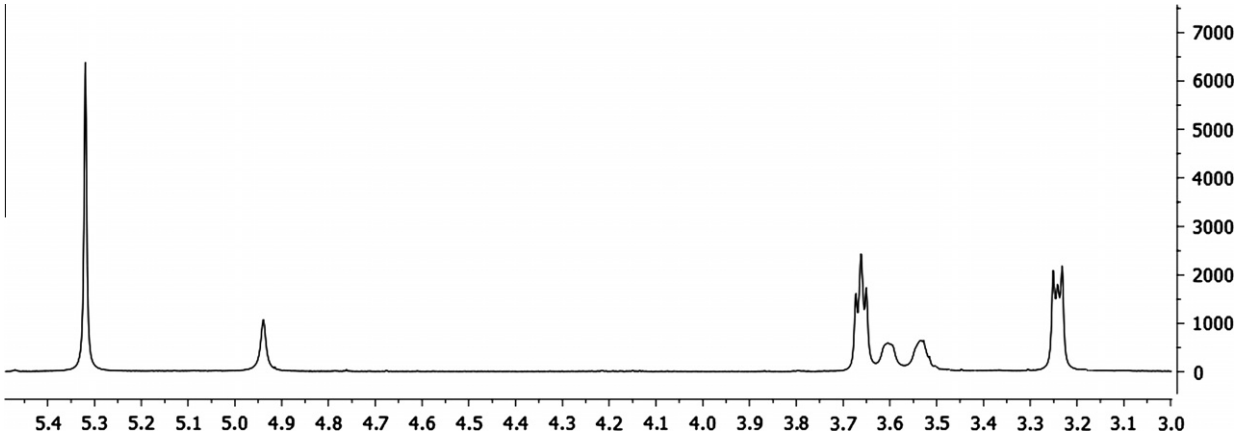


Fig. 4. Detail of the ^{1}HNMR spectrum of benzamide **1g** showing line broadening.

that benzamide **1d** shows an intermediate *E/Z* ratio between formamide **1a** and acetamide **1b**. This apparently lower effective size of the phenyl might be a consequence of a larger N–CO bond distance due to cross conjugation or may alternatively be indicative of additional (non purely steric) interactions.

Introduction of a halogen atom in the 4′ position of the *N*-aryl group also increases the *Z* preference. The proportion is roughly the same for acetamides and formamides, independently of the nature of the halogen. The same trend is evident when comparing benzamides **1h** and **1g**, indicating that replacement of a phenyl by a *p*-tolyl group has little influence on the *E/Z* ratio.

When compared with the corresponding homologous hexahydropyrimidines **2** [15] (Table 5), compounds **1** show a greater *Z* preference regardless of the nature of the R and *N*-Ar substituents, indicative of a clear ring size effect. Moreover, this change in the ring size influences unevenly the effects of the R and *N*-Ar substituents on the *E/Z* equilibrium: in hexahydropyrimidine derivatives, the *Z* preference increases gradually in the series H < Me < Et < iPr [15], wich somehow differs from the previously discussed behavior of compounds **1a–c**. In addition, in the hexahydropyrimidine derivatives, benzamide **2d** has approximately the same *E/Z* ratio than formamide **2a**, at variance with the corresponding hexahydro diazepines.

4. Conclusions

We report here the complete ^{1}H and ^{13}C NMR characterization of a series of 1-acyl-3-arylhexahydro-1,3-diazepines **1**. Such compounds display *E/Z* isomerism due to partial (O)C–N double bond character, showing two unequally populated sets of signals in their ^{1}H and ^{13}C NMR spectra. The ^{1}H NMR resonances of both rotamers of some selected compounds were assigned on the basis of ASIS effects and the assignments confirmed by NOESY. ^{13}C NMR signals were attributed by HSQC experiments for **1a,b,g**. For all the compounds, the *E/Z* equilibrium favours the *Z* diastereoisomer. This preference is sensitive to steric hindrance in the carbonyl substituent R, and, to a lesser extent, to electron withdrawing groups in the *N*-aryl. A comparison with the corresponding six membered aminals shows the existence of a ring size effect which enhances the preference for the Z rotamer.

To our knowledge, this is the first stereochemical study on this novel family of seven membered heterocyclic compounds and one of the few reports on hexahydrodiazepines in the literature.

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