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E/Z equilibrium in tertiary amides. Part 2: *N*-acyl-*N*′-arylhexahydropyrimidines

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ABSTRACT

The ^{1}H and ^{13}C NMR spectroscopic study of a series of novel *N*-acyl-*N*′-arylhexahydropyrimidines **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 the 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 and HMBC experiments. The detailed conformational study of two representative members was performed employing the *ab initio* RHF/6-311G++ method. The influence of steric and electronic features of the *N*-substituents on the relative populations of *E/Z* rotamers is also analyzed.

1. Introduction

Cyclic aminals are compounds of interest due to their pharmacological and chemical properties. The five membered heterocyclic aminal (imidazolidine) core is found in many bioactive compounds like antiinflammatory and analgesic agents [1], fungicides, antibacterials, parasiticides and antivirals [1,2]. Six membered cyclic aminals (hexahydropyrimidines) also show biological activity as analgesics, parasiticides [3], antifungals and antibacterials [4]. Besides, hexahydropyrimidines also behave as prodrugs of pharmacologically active di [5] and polyamines [6]. Such compounds have recently been applied as pro-perfumes, in the controlled release of volatile aldehydes and ketones [7]. In synthetic organic chemistry, cyclic aminals are useful as protecting groups in the selective functionalization of di and polyamines.

Structural features of amides have been widely studied by NMR spectroscopy and molecular modeling, as they represent model compounds for the peptide bond [8]. In particular, the *E/Z* equilibrium in heterocyclic tertiary amides and related compounds has been reviewed [9]. 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 [10], while *E/Z* isomerization is a key process involved in protein folding and biocatalysis [11].

The partial double bond character of the (O)C–N bond in amides causes a substantial rotational barrier, which ranges between 15 and 23 kcal/mol [12,13]. 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.

The absence of literature data on the stereochemistry of *N*-acyl derivatives of cyclic aminals led us to investigate the *E/Z* equilibrium in compounds **1** employing NMR spectroscopy and theoretical methods, as part of ongoing research on nitrogen heterocycles with hindered rotation [14–17].

2. Experimental

2.1. Chemistry

Compounds **1a–i** were prepared by condensation of the corresponding *N*-acyl-*N*′-aryl-1,3-propanediamines [18,19] and excess aqueous formaldehyde. A methanolic solution of the reactants was stirred at room temperature for 12–36 h. The desired compounds were purified by column chromatography. Yields and analytical data of compounds **1a–i** are as follows.

1-Formyl-3-(4-chlorophenyl)hexahydropyrimidine (**1a**) was obtained as an oil (69%). MS (EI), *m*/z 224 ($M^{+\cdot}$). Anal. Calcd. for $C_{11}H_{13}ClN_2O$: C, 58.80; H, 5.83; N, 12.47, found: C, 58.71; H, 5.91; N, 12.42.

1-Acetyl-3-(4-chlorophenyl)hexahydropyrimidine (**1b**) was obtained as a white solid (64%), Mp 60–62 °C (cyclohexane). MS (EI), *m*/z 238 ($M^{+\cdot}$). Anal. Calcd. for $C_{12}H_{15}ClN_2O$: C, 60.38; H, 6.33; N, 11.73, found: C, 60.24; H, 6.39; N, 11.76.

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1-Propionyl-3-(4-chlorophenyl)hexahydropyrimidine (**1c**) was obtained as an oil (61%). MS (EI), *m*/z 252 ($M^{+\cdot}$). Anal. Calcd. for $C_{13}H_{17}ClN_2O$: C, 61.78; H, 6.78; N, 11.08, found: C, 61.71; H, 6.82; N, 11.10.

1-Isobutyryl-3-(4-chlorophenyl)hexahydropyrimidine (**1d**) was obtained as an oil (16%). MS (EI), *m*/z 266 ($M^{+\cdot}$). Anal. Calcd. for $C_{14}H_{19}ClN_2O$: C, 63.03; H, 7.18; N, 10.50, found: C, 62.94; H, 7.21; N, 10.45.

1-Formyl-3-phenylhexahydropyrimidine (**1e**) was obtained as a white solid (64%), Mp 68–70 °C (cyclohexane). MS (EI) *m*/z 190 ($M^{+\cdot}$). Anal. Calcd. for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.72, found: C, 69.38; H, 7.45; N, 14.68.

1-Acetyl-3-phenylhexahydropyrimidine (**1f**) was obtained as an oil (63%). MS (EI), *m*/z 204 ($M^{+\cdot}$). Anal. Calcd. for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.89; N, 13.71, found: C, 70.42; H, 7.94; N, 13.73.

1-Acetyl-3-(4-methoxyphenyl)hexahydropyrimidine (**1g**) was obtained as an oil (49%). MS (EI), *m*/z 234 ($M^{+\cdot}$). Anal. Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96, found: C,66.58; H, 7.79; N, 11.94.

1-Benzoyl-3-(4-chlorophenyl)hexahydropyrimidine (**1h**) was obtained as a white solid (68%), Mp 86–88 °C (cyclohexane). MS (EI), *m*/z 300 ($M^{+\cdot}$). Anal. Calcd. for $C_{17}H_{17}ClN_2O$: C, 67.88; H, 5.70; N, 9.31, found: C, 67.79; H, 5.76; N, 9.30.

1-Acetyl-3-(2-chlorophenyl)hexahydropyrimidine (**1i**) was obtained as an oil (71%). MS (EI), *m*/z 238 ($M^{+\cdot}$). Anal. Calcd. for $C_{12}H_{15}ClN_2O$: C, 60.38; H, 6.33; N, 11.73, found: C, 60.29; H, 6.37; N, 11.70.

2.2. Spectra

^1H and ^{13}C NMR 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), quartet (q), heptet (h), multiplet (m) and broad signal (bs). HSQC, HMBC and phase-sensitive NOESY spectra were recorded on a Bruker Avance II 500 spectrometer.

2.3. Computational study

Input geometries for both rotamers of compounds **1e,f** were preoptimized with the semiempirical method AM1. Structures thus obtained were then optimized with the HF/3-21G method. The resulting minima were further optimized either with the *ab initio* HF (6-31G** or 6-311G** basis sets) or DFT B3LYP/6-311G** methods [20]. The resulting minima were subjected to frequency calculations with non-imaginary frequencies obtained.

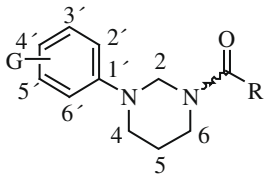
3. Results and discussion

The compounds described in this work are shown in Table 1. ^1H NMR chemical shifts, multiplicities and relative populations of *E/Z* diastereomers of compounds **1a–i** ($CDCl_3$) are given in Table 2. ^1H NMR chemical shifts, multiplicities and relative populations of *E/Z* diastereomers of compounds **1a,b,i** (C_6D_6) are given in Table 3. ^{13}C NMR chemical shifts of compounds **1a–i** ($CDCl_3$) are given in Table 4.

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 corresponding to both stereoisomers, unless the equilibrium is highly biased towards one of them. As expected, two unequally populated sets of signals are present in the spectrum of **1a**, corresponding to *E/Z* diastereoisomers. The multiplicity of the signals indicates that ring inversion is 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 data previously reported for *N*-aryl-*N′*-alkylhexahydropyrimidines [21] and for *N,N′*-dimethylhexahydropyrimidine [22]. Like many other compounds, amides display the so called ASIS (anisotropic solvent induced shifts) effect [23]. Interestingly, 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 [12]. This effect can be diagnostic for the differential assignment of *cis* and *trans* *N*-substituents, and in our experience is more reliable than assignment derived from chemical shifts in model compounds, specially for amides containing additional anisotropic substituents [24]. Following this criterion, in compound **1a**, the singlet corresponding to the major diastereoisomer was attributed to the *cis* *N*-methylene group, and the one corresponding to the minor species as *trans* to the carbonyl oxygen ($\Delta\delta = -0.33$ and -0.83 ppm, respectively). Signals corresponding to positions 4 and 6 of the major diastereoisomer partially overlap in the spectrum run in $CDCl_3$. The first one ($\delta = 3.57$ ppm) was tentatively attributed to methylene 6. Such resonance experiences a stronger diamagnetic shift in C_6D_6 than the triplet corresponding to the minor species ($\Delta\delta = -0.73$ and -0.37 ppm, respectively), and was attributed to the *N*-methylene *trans* to the oxygen. The remaining signals were attributed to the major and minor species on the basis of their relative integration. This tentative assignment was confirmed in the NOESY spectrum of **1a** (Fig. 1), which also confirmed the assignment of positions 4 and 6 of both species. 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 and HMBC spectra. The ^1H and ^{13}C NMR signals of formamide **1e** were attributed by analogy. In both cases, a slight preference for the *Z* stereoisomer is observed.

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–d** all display two unequally populated sets of signals. Resonances of amide *N*-methylenes (positions 2 and 6) of **1b** were attributed on the basis of their $\Delta\delta$. Thus, the singlet corresponding to the major diastereoisomer ($\delta = 4.96$ ppm) was attributed to the methylene group *cis* to the carbonyl oxygen,

Table 1
N-acyl-*N′*-arylhexahydropyrimidines **1a–i**.



Compound **1**	G	R
a	4-Cl	H
b	4-Cl	CH_3
c	4-Cl	C_2H_5
d	4-Cl	*iso*-C_3H_7
e	H	H
f	H	CH_3
g	4-OCH_3	CH_3
h	4-Cl	C_6H_5
i	2-Cl	CH_3

Table 2
^{1}H NMR signals and relative populations of compounds **1a–i** ($CDCl_3$).

Compd.	2	6	4	5	Aromatics	R	%
1a (*Z*)	4.92 (s)	3.57 (t, 5.8)[a]	3.59 (t, 5.8)[b]	1.72–1.76 (m)	2′,6′: 6.96 (d, 9.0) 3′,5′: 7.23 (d, 9.0)	8.04 (s)	61
1a (*E*)	4.68 (s)	3.70 (t, 5.5)	3.49 (t, 5.6)	1.77–1.82 (m)	2′,6′: 6.86 (d, 9.0) 3′,5′: 7.26 (d, 9.0)	8.19 (s)	39
1b (*Z*)	4.96 (s)	3.61 (t, 5.7)	3.51 (t, 5.5)	1.70–1.75 (m)	2′,6′: 6.94 (d, 8.9) 3′,5′: 7.18 (d, 8.9)	2.09 (s)	72
1b (*E*)	4.73 (s)	3.71 (t, 5.8)	3.36 (t, 5.6)	1.76–1.81 (m)	2′, 6′: 6.86 (d, 8.8) 3′,5′: 7.24 (d, 8.8)	2.16 (s)	28
1c (*Z*)	4.96 (s)	3.60 (t, 5.7)	3.49 (t, 5.5)	1.69–1.74 (m)	2′,6′: 6.93 (d, 8.9) 3′,5′: 7.18 (d, 8.9)	2.32 (q, 7.4) 1.13 (t, 7.4)	74
1c (*E*)	4.71 (s)	3.70 (t, 5.8)	3.37 (t, 5.5)	1.69–1.74 (m)	2′,6′: 6.86 (d, 8.8) 3′,5′: 7.23 (d, 8.8)	2.41 (q, 7.4) 1.13 (t, 7.4)	26
1d (*Z*)	4.99 (s)	3.68 (t, 5.6)	3.53 (t, 5.5)	1.71–1.75 (m)	2′,6′: 6.94 (d, 9.0) 3′,5′: 7.20 (d, 9.0)	2.78 (h, 6.8) 1.13 (d, 6.8)	76
1d (*E*)	4.76 (s)	3.72 (bs)	3.35 (bs)	1.81 (bs)	2′,6′: 6.87 (d, 8.3) 3′,5′: 7.25 (d, 8.3)	2.88 (bs) 1.13 (d, 6.8)	24
1e (*Z*)	4.69 (s)	3.51–3.56 (m)	3.50–3.61 (m)	1.71–1.79 (m)	2′,4′,6′: 6.85–7.04 (m) 3′,5′: 7.23–7.32 (m)	8.02 (s)	52
1e (*E*)	4.86 (s)	3.68 (t, 5.9)	3.51–3.56 (m)	1.71–1.80 (m)		8.17 (s)	48
1f (*Z*)	4.99 (s)	3.67 (t, 5.8)	3.53 (t, 5.5)	1.70–1.74 (m)	7.02 (d, 8.7) 6.85 (t, 7.3) 7.23–7.32 (m)	2.09 (s)	63
1f (*E*)	4.76 (s)	3.61 (t, 5.8)	3.39 (t, 5.6)	1.76–1.80 (m)	6.94 (d, 8.7) 7.23–7.32 (m)	2.18 (s)	37
1g (*Z*)	4.87 (s)	3.69 (t, 5.8)	3.41 (t, 5.4)	1.71–1.78 (m)	2′, 6′: 6.85 (d, 7.2) 3′,5′: 6.93 (d, 7.2) OCH_3: 3.75 (s)	2.10 (s)	61
1g (*E*)	4.73 (s)	3.59 (t, 5.8)	3.27 (t, 5.5)	1.71–1.78 (m)	2′, 6′: 6.82 (d, 7.2) 3′,5′: 6.97 (d, 7.2) OCH_3: 3.78 (s)	2.15 (s)	39
1h (*Z*)	5.11 (bs)	3.87 (bs); 3.54 (bs); 3.43 (bs)	1.64 (bs)	6.50 (bs) 7.01–7.21 (bs, m)	7.40 (bs)	59[b]	
1h (*E*)	4.69 (bs)		1.89 (bs)	6.50 (bs) 7.01–7.21 (bs, m) 7.40 (bs)	7.40 (bs)	41[b]	
1i (*E*)	4.59 (s)	3.73 (t, 5.8)	3.41 (t, 5.4)	1.80–1.86 (m)	6.93–7.41 (m)	2.12 (s)	56
1i (*Z*)	4.86 (s)	3.64–3.70 (m)	3.28 (t, 5.4)	1.69–1.76 (m)	6.93–7.41 (m)	2.15 (s)	44

[a] Partially overlapping signals.
[b] Integration is approximate due to line broadening.

Table 3
^{1}H NMR signals and relative populations of compounds **1a**,**b**,**i** (C_6D_6).

Compd.	2	6	4	5	Aromatics	R	%
1a (*Z*)	4.59 (s)	2.84 (t, 5.5)	2.53 (t, 5.8)	0.85–0.92 (m)	2′, 6′: 6.79 (d, 6.8); 3′, 5′: 7.15–7.24 (m)	7.65 (s)	57
1a (*E*)	3.85 (s)	3.33 (t, 5.8)	2.68 (t, 5.5)	1.07–1.14 (m)	2′, 6′: 6.32 (d, 9.0); 3′, 5′: 7.15–7.24 (m)	7.91 (s)	43
1b (*Z*)	4.79 (s)	2.86 (t, 5.5)	2.71 (t, 5.8)	0.97–0.99 (m)	2′, 6′: 6.87 (d, 9.0); 3′, 5′: 7.15–7.19 (m)	1.65 (s)	70
1b (*E*)	4.07 (s)	3.51 (t, 5.7)	2.67 (t, 5.5)	1.25–1.27 (m)	2′, 6′: 6.39 (d, 8.8); 3′, 5′: 7.15–7.19 (m)	1.80 (s)	30
1i (*E*)	4.01 (s)	3.51 (t, 5.8)	2.68 (t, 5.6)	1.27–1.35 (m)	7.12–7.24 (m); 6.76–6.99 (m); 6.58–6.68 (m)	1.83 (s)	60
1i (*Z*)	4.75 (s)	3.05 (t, 5.5)	2.68 (t, 5.6)	0.98–1.08 (m)	7.12–7.24 (m); 6.76–6.99 (m); 6.58–6.68 (m)	1.63 (t)	40

and the one corresponding to the minor species (δ = 4.73 ppm) to the *trans* methylene ($\Delta\delta$ = −0.17 and −0.66 ppm, respectively). Conversely, triplets at 3.61 and 3.71 ppm were assigned as *trans* and *cis* *N*-methylenes ($\Delta\delta$ = −0.75 and −0.20 ppm, respectively). 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. 1). ^{1}H NMR spectra of hexahydropyrimidines **1c,d** are similar to that of compound **1b**, and were assigned by analogy (Table 2). Interestingly, in compound **1d** the signals of the minor species display line broadening. This feature, absent in the major diastereoisomer, may indicate that a dynamic process different from *E*/*Z* interconversion, probably ring inversion, is rather slow in the NMR timescale at room temperature. The previous assignment was confirmed by NOESY for propionamide **1c** and isobutyramide **1d** (Fig. 1). For compounds **1b–d**, unambiguous differential assignment of the ^{13}C resonances of both rotamers (Table 4) was performed on the basis of the correlations observed in their

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

Compd.	2	6	4	5	R	1′	2′,6′ 3′,5′	4′	C=O
1a (*Z*)	57.73	45.43	50.20	23.85	–	146.44	118.32 129.27	125.87	160.73
1a (*E*)	64.76	39.63	49.65	23.13	–	146.68	118.25 129.42	125.26	160.54
1b (*Z*)	59.24	46.09	49.38	23.72	21.25	146.40	117.95 129.15	124.68	170.18
1b (*E*)	66.95	41.52	49.10	23.72	21.35	147.32	118.52 129.32	125.39	168.95
1c (*Z*)	59.55	45.20	49.46	23.82	9.24 26.33	146.86	117.93 129.15	124.67	172.39
1c (*E*)	65.10	41.67	49.26	23.82	9.24 26.33	147.46	118.51 129.31	ND	ND
1d (*Z*)	59.58	45.20	49.62	23.94	19.12 29.96	146.82	117.91 129.06	124.55	175.45
1d (*E*)	64.98	41.68	49.31	23.94	19.12 29.61	ND	118.46 129.23	ND	ND
1e (*Z*)	57.80	45.40	49.95	23.94	–	147.84	116.99 129.32	120.27	160.65
1e (*E*)	64.72	39.63	49.50	23.20	–	148.02	116.93 129.43	120.79	160.57
1f (*Z*)	59.33	46.01	49.13	23.77	21.18	148.13	116.63 129.21	119.82	168.97
1f (*E*)	66.01	41.52	48.95	23.67	21.18	148.61	117.23 129.33	120.82	168.97
1g (*Z*)	60.44	45.86	50.04	23.67	21.17	142.15	118.52 114.34	153.58	168.84
1g (*E*)	67.40	41.28	50.18	23.80	21.17	142.63	119.61 114.43	154.46	168.93
1h (*Z*)	66.70*	49.70*		23.79*	135.22*	146.67*	118.01*	126.98*	170.28*
1h (*E*)	60.15*	48.65* 47.56*			129.96* 128.42*		129.08*	125.02*	
1i (*E*)	66.55	40.97	50.61	24.07	21.15	146.27	128.80 127.58 121.44 130.39	124.58	168.88
1i (*Z*)	60.96	45.62	50.42	24.12	21.35	146.55	128.03 127.35 121.50 130.51	123.73	168.51

* Broad signal.

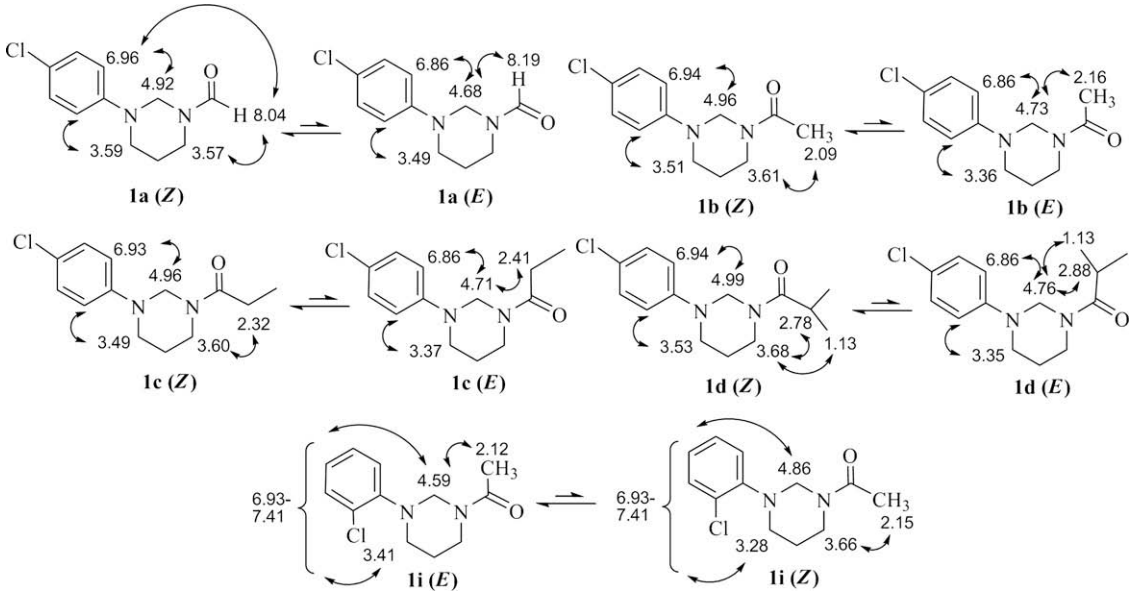


Fig. 1. Relevant correlations observed in the NOESY spectra ($CDCl_3$) of compounds **1a–d,i**.

HSQC and HMBC spectra, while acetamides **1f,g** were assigned by analogy.

At variance with the previous examples, in the ^1H and ^{13}C NMR spectra of benzoyl derivative **1h** the signals of both species show

significant line broadening, indicative of a lower barrier for the interconversion of the *E/Z* diastereoisomers. This feature was previously observed for 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 [12].

In all the previous cases, the *Z* diastereoisomer was the predominant species. Quite surprisingly, this preference is reversed in acetamide **1i**, bearing an *ortho* substituent in the *N*-aryl. Applying the $\Delta\delta$ criterion for **1i**, singlets at 4.59 ppm ($\Delta\delta = -0.58$ ppm) and 4.86 ppm ($\Delta\delta = -0.11$ ppm) were respectively assigned as *trans* and *cis* to the carbonyl oxygen. Conversely, signals centered at 3.73 and 3.67 ppm were assigned as *cis* and *trans* *N*-methylenes ($\Delta\delta = -0.22$ and -0.62 ppm, respectively). The remaining resonances in **1i** were attributed to the major and minor rotamers on the basis of their relative integration. The assignment was confirmed by the correlations observed in the NOESY spectrum of **1i** (Fig. 1).

Two model compounds were investigated computationally, namely acetamide **1f** and formamide **1e**. For compound **1f**, results employing the HF *ab initio* method applying either the 3-21G, 6-31G** or 6-311G** basis sets were compared with those obtained with the DFT B3LYP 6-311G** method. Four initial minima were identified for each rotamer at the AM1 level. After HF/3-21G optimization, only two minima were located for each distereoisomer, which were then optimized with the indicated *ab initio* or DFT methods. For each rotamer, the two minima were labelled as *A* and *B*. Structures obtained at the HF/6-311G** level for **1f** are shown in Fig. 2. In all cases, the heterocyclic ring has approximately a chair conformation, distorted by the nitrogen atoms bearing π-conjugating substituents. Relative energies for the different conformations are shown in Table 5. The *E/Z* $\Delta\Delta$Hf was estimated in each case considering the more stable conformations, being the *Z* rotamer always preferred. The magnitude of the energy differences either between two conformations of the same rotamer or between *E/Z* rotamers varies according to the method employed for the calculation. It is clearly overestimated with the 3-21G basis set, which predicts an *E/Z* difference above 2 kcal mol^{-1}. The calculated gap decreases on going from 3-21G → 6-31G** → 6-311G** and also comparing B3LYP/6-311G** and HF/6-311**G methods. The best agreement between experimental results and calculations is found with the *ab initio* HF/6-311G** method. The same analysis performed on formamide **1e** with the HF/6-311G** method led to analogous results, being the energy differences between conformers and also between *E/Z* rotamers lower than for acetamide **1f** (Table 5). The calculated *E/Z* $\Delta\Delta$Hf values are in line with the experimental trends (relative populations) measured by integration of the ^{1}H NMR signals for **1e,f** (Table 2).

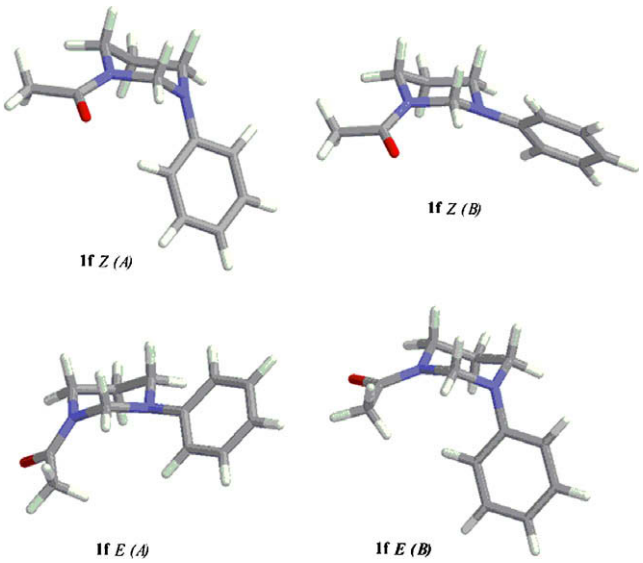


Fig. 2. Conformational minima for compound **1f** at the HF/6-311G** level.

Table 5
Relative energies (kcal mol^{-1}) for the conformational minima of compounds **1f,e**.

Compd.	Structure	ΔHf[a]	ΔHf[b]	ΔHf[c]	ΔHf[d]
1f	*Z* (*A*)	0	0	0	0
	Z (*B*)	4.56	1.65	1.40	1.48
	E (*A*)	2.45	0.98	0.67	0.97
	E (*B*)	3.48	1.58	1.44	1.88
1e	*Z* (*A*)	–	–	0	–
	Z (*B*)	–	–	0.26	–
	E (*A*)	–	–	0.55	–
	E (*B*)	–	–	0.97	–

[a] HF/3-21G.
[b] HF/6-31G**.
[c] HF/6-311G**.
[d] B3LYP/6-311G**.

Analysis of data reported in Table 2 shows that the relative populations of *E/Z* rotamers are influenced by the nature of both *N*-substituents. The preference for the *Z* diastreoisomer in *N*-(4-chlorophenyl) hexahydropyrimidines **1a–d** increases with increasing volume of the carbonyl substituent R in the series H < CH_3 < C_2H_5 < *iso*-C_3H_7. The *E/Z* ratio is also sensitive to steric and electronic features of substituents in the aryl moiety. A comparison between acetamides **1b,f,g** shows that *para* substitution with an electron donor does not influence significatively the *E/Z* equilibrium, which is more shifted towards the *Z* rotamer in the 4-chloro derivative (**1b**). The same effect is observed in formamides **1a,e**. Steric hindrance in the aryl moiety (compound **1i**) clearly destabilizes the *Z* diastereoisomer, which becomes the minor species. This change may be the result of a twisted conformation for the aryl group in the ground state.

4. Conclusions

We performed the ^{1}H and ^{13}C NMR spectroscopic study of a series of novel tertiary amides derived from the hexahydropyrimidine core. The compounds under study display *E/Z* isomerism due to restricted (O)C–N rotation, 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 **1a,b,i** were assigned on the basis of ASIS effects and the assignments confirmed by NOESY. ^{13}C NMR signals were attributed by HSQC and HMBC experiments for **1a–d**. In general, the *E/Z* equilibrium favours the *Z* diastereoisomer. This preference was accentuated with increasing steric hindrance in the carbonyl substituent R, and also by electron withdrawing groups in the *N*-aryl. The *E/Z* ratio was reversed in the compound bearing an *ortho* substituent in the aryl group. Results of the complete conformational study of compounds **1f,e** performed with the *ab initio* HF/6-311G** method were in good agreement with the experimentally determined *E/Z* ratios.

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