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Synthesis and conformational analysis of chiral ureas incorporating *N*-1-phenylethyl groups. Manifestation of allylic 1,3-strain†

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ABSTRACT: The synthesis of novel chiral ureas (*R*,*R*)-**2**, (*S*,*S*)-**3** and (*R*)-**6** incorporating the α-phenylethyl group is described. Conformational analysis of these ureas, and of previously reported (*R*,*R*)-**1**, was carried out computationally, both at semiempirical (AM1 and PM3) and *ab initio* (HF and B3LYP) levels, and experimentally from x-ray crystallographic analysis of (*R*,*R*)-**2** and (*S*,*S*)-**3**, and in the case of (*R*)-**6** by means of NOE NMR spectroscopy. A substantial preference of 1.5–2.6 kcal mol^{-1} in favor of conformations with *syn*-periplanar arrangements between the C—H bond at the α-phenylethyl *N*-substituent and the N—C(O) segment was found, and this observation confirms the relevance of allylic $A^{1,3}$ strain in this system. The possibility of hydrogen bonding in the *syn*-periplanar C—H···O═C—N arrangement was discarded in the light of topological analysis of (*R*,*R*)-**1**, within the frame of Bader's atoms in molecules theory. Copyright © 2005 John Wiley & Sons, Ltd.

KEYWORDS: chiral ureas; conformational analysis; allylic 1,3-strain; theoretical chemistry; density functional theory; *ab initio* calculations

INTRODUCTION

Urea and its derivatives constitute an important class of organic compounds with a great variety of applications in fundamental and applied science. They find extensive application as antioxidants in gasoline,[1] dyes for cellulose fibers,[1] non-linear optical devices,[2] resin precursors[3] and synthetic intermediates.[4] Moreover, the presence of the urea moiety in many biologically important natural compounds, such as nucleotides, vitamin B_{13} and enzymes,[5] renders it a subject of great interest in biochemistry and related areas. Furthermore, urea-based drugs have been developed that are effective antitumor agents[6] and HIV protease inhibitors.[7] Finally, the anion binding properties of urea, owing to its ability to form two hydrogen bonds,[8] have been exploited in several relevant areas such as anion recognition and sensing,[9] enantioselective asymmetric synthesis[10] and kinetic resolution of chiral compounds.[11]

In this context, the synthesis of new chiral ureas (*R*,*R*)-**1** and (*S*,*S*)-**1**, incorporating the 1-phenylethyl group at the *N*-atoms was recently reported[12] [Scheme 1(a)]. The potential of these chiral Lewis bases as promoters of stereoselective reactions will depend on the possibility that the *N*-1-phenylethyl chiral adjuvant (for recent reviews on applications of 1-phenylethylamine in the preparation of enantiomerically pure compounds, see Ref. 13) adopts a single or predominant conformation in the molecule. In particular, conformations presenting coplanar orientation between the C—H bond and the N—C(O) segment should be preferred in order to prevent allylic $A^{1,3}$ strain,[14] which would be present in the other possible conformations around the N—CHMePh bond. Indeed, N → C═O conjugation in the urea segment effectively places the phenethyl group in an allylic-like position, so that the C—H bond, being the smallest substituent at the stereogenic carbon, should adopt a *syn*-periplanar arrangement in relation to the N—C(O) segment [Scheme 1(b)].

This paper concerns the preparation and conformational analysis of several chiral ureas structurally related to **1**.

RESULTS AND DISCUSSION

Preparation of chiral ureas 2–5

Acyclic chiral urea (*R*,*R*)-**2** was obtained by reaction of (*R*)-1-phenylethylamine with triphosgene in the presence

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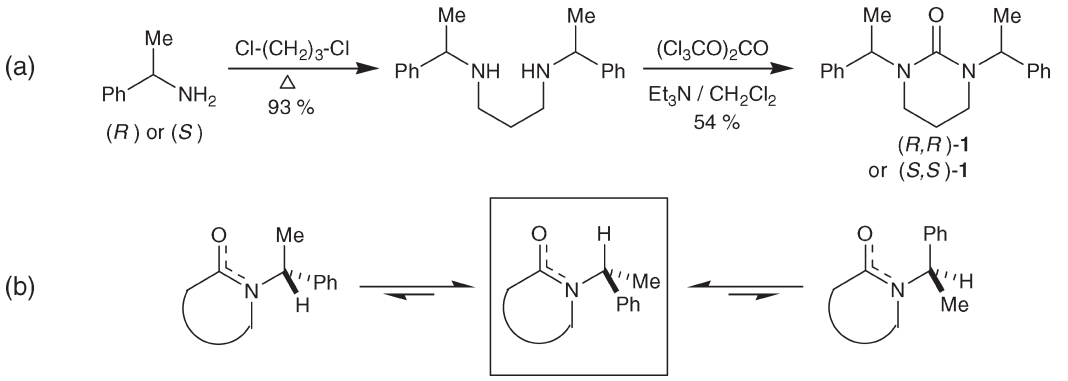


Scheme 1

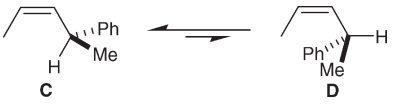
of triethylamine and methylene chloride as solvent, according to the procedure described in the literature[15] [Scheme 2(a)]. Similarly, *N*,*N*′-bis[(*S*)-1-phenylethyl]ethane-1,2-diamine[16] was the starting material for the preparation of five-membered urea (*S*,*S*)-**3** [Scheme 2(b)]. Non-C_2-symmetric chiral urea (*R*)-**6** was synthesized from acrylonitrile via conjugate addition of (*R*)-1-phenylethylamine followed by catalytic hydrogenation and condensation with triphosgene [Scheme 2(c)].

Conformational analysis

N,*N*′-Bis[(*R*)-1-phenylethyl]propyleneurea, (*R*,*R*)-1

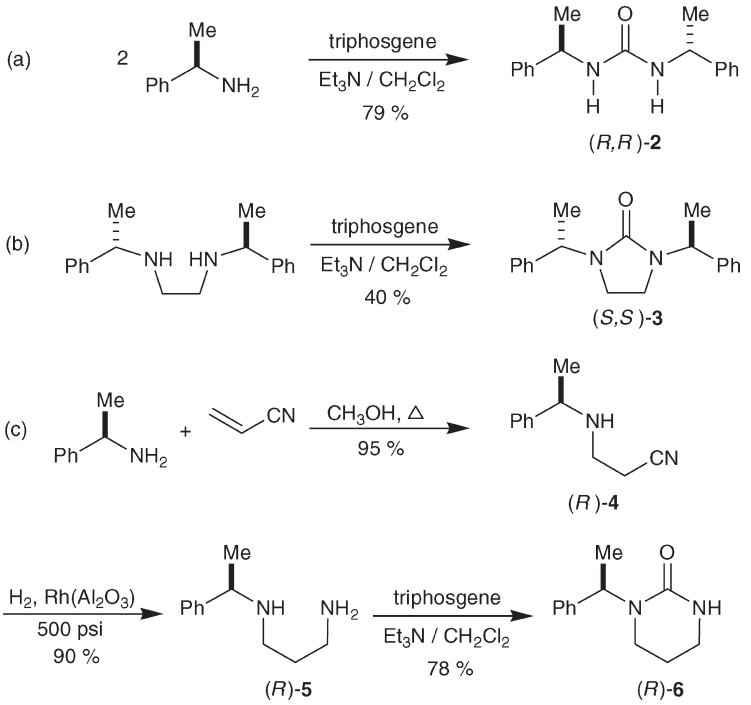
As expected from allylic A[1,3] strain, x-ray analysis of single crystals of (*R*,*R*)-**1** showed an orientation of the 1-phenylethyl groups in which the C—H bonds are nearly *syn*-periplanar to the N—C(O) segment.[12] This solid-state conformation is also predicted to be the most stable in the gas phase, at various levels of theory (Table 1).

All *ab initio* methods predict conformation **A** to be significantly more stable than conformation **B**, by 2.2–2.6 kcal mol^{-1} (1 kcal = 4.184 kJ). For comparison, Broeker *et al.*[17] calculated (4*S*)-phenyl-(2*Z*)-pentene to prefer the a *syn*-periplanar (C═C/C—H) arrangement **C** by 1.5 kcal mol^{-1} over arrangement **D** [Eqn (1)]:



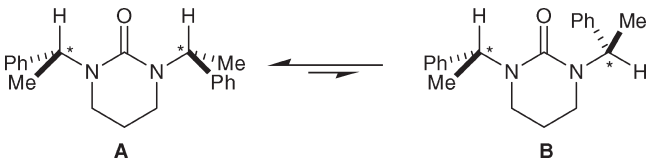
(1)

whereas Tietze and Schulz[18] found from *ab initio* calculations on 3-methyl-1-butene rotamer **E** (*syn*-periplanar



Scheme 2

Table 1. Calculated (gas-phase) conformational preference of the *N*-(1-phenylethyl) *N*-substituents in (*R*,*R*)-**1**



Method	ΔE (kcal mol^{-1})	Dihedral [H—C*—N—C(O)] angles (°)	
		A	**B**
AM1	1.69	28.9 and 26.5	28.6 and −163.7
PM3	1.27	27.1 and 32.4	34.0 and −176.7
HF/3–21G	2.19	14.7 and 14.9	5.9 and −165.1
HF/6–31G**	2.54	2.9 and −14.5	−3.6 and 170.4
B3LYP/6–31G*	2.35	3.0 and 7.9	2.8 and −169.4
B3LYP/6–31G**	2.33	3.0 and 7.6	2.8 and −170.1
B3LYP/6–311+G**//B3LYP/6–31G*	2.59	3.0 and 7.9	2.8 and −169.4

orientation between the C═C double bond and the methine C—H bond) to be 2.48 kcal mol^{-1} more stable than rotamer **F** (*anti*-periplanar orientation) [Eqn (2)]:

(2)

The experimentally obtained [x-ray diffraction analysis of crystalline (*R*,*R*)-**1**; see Ref. 12] interatomic distance between the carbonyl oxygen and the methine C—H hydrogen on the 1-phenylethyl group is 2.27 Å, which is less than the sum of the atomic van der Waals radii for oxygen and hydrogen, 1.50 and 1.20 Å, respectively.[19] Hence the possibility of the existence of a hydrogen bonding interaction that could contribute to the stabilization of conformer **A** in the equilibrium depicted in Table 1 was considered. Nevertheless, it must be pointed out that two recent, high-level theoretical studies[20] of the *N*-methyl rotational barriers in amide and urea derivatives concluded that staggered conformers **G** are 0.3–0.8 kcal mol^{-1} more stable than conformers **H** [Eqn (3)], in which one could expect that hydrogen bonding stabilization would be more efficient.

(3)

To obtain information regarding the nature of the C—H···O═C interaction in **A** (Table 1), theoretical analysis within the frame of the topological theory of atoms in molecules[21] was carried out. The AIM2000[22] set of programs was used, obtaining the properties of atoms and critical points (cps) in the charge density: electron density (ρ), Laplacians ($\nabla^2\rho$) and ellipticities (ε).

Two of the most important contributions of the AIM theory are the precise definition of an atom in a molecule and the definition of the chemical bond. These concepts correspond to the topological properties of the electron density.[21] The chemical structure of a molecule is unambiguously described determining the critical points through the electron density (ρ) and corresponds to the gradient zero density points. These points, and also the first and second derivatives, can be determined with the use of the AIM2000[22] program. From the second derivative, it is possible to determine the three principal curvatures associated with a critical point due to its index (the algebraic addition of the curvature sign). In addition to density, ellipticity is an important property of a critical point. This is defined as the coefficient of the negative curves along the perpendicular axis to the bonding path, $\varepsilon = \lambda(1)/\lambda(2) - 1$, and should be considered as an index of a bond's anisotropy.

Figure 1 shows the calculated C—H···O═C bond trajectories and critical points between atoms in the electron density analysis of (*R*,*R*)-**1**. Most relevant, the C—H···O═C bond trajectories present low electronic

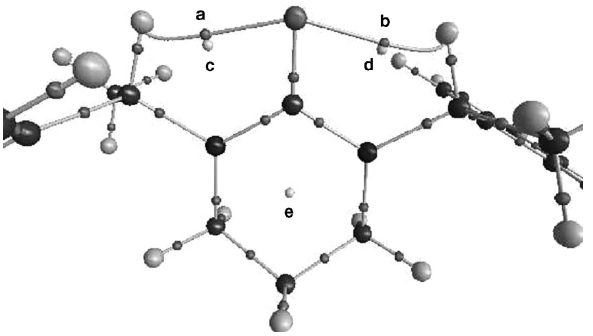


Figure 1. Critical points and bonding trajectories in the electron density of (*R*,*R*)-**1** calculated at the HF/6–311+G**//HF/6–31G** level of theory (for clarity, Ph groups have been deleted)

Table 2. Properties of critical points associated with weak interactions in (*R*,*R*)-**1** (see Fig. 1)

Point	ρ (e Å^{-3})	ϵ	x^a	y^a	z^a
a^b	0.022	1.865	−0.0230	−0.0080	0.1326
b^b	0.0213	3.752	−0.0221	−0.0046	0.1301
c^c	0.0215		−0.022	0.0097	0.1272
d^c	0.0213		−0.0215	0.0052	0.1275
e^c	0.0197		−0.0148	0.0769	0.0825

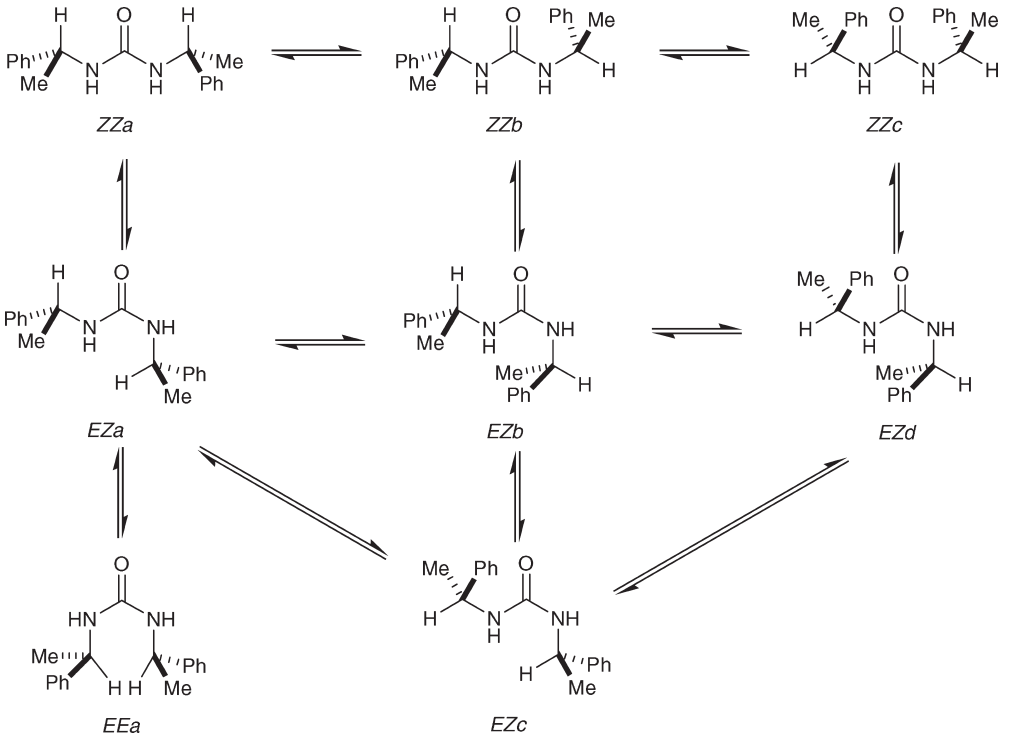
[a] Eigenvalues of the Hessian at critical point.
[b] Critical bond point (3, −1).
[c] Critical ring point (3, +1).

density at the critical points *a* and *b* ($\rho = 0.022$ and 0.021 e Å^{-3}, respectively) which is indicative of a very weak bonding interaction. In contrast, bonding interactions are usually associated with much larger electronic densities; for example, a typical A—H···B hydrogen bond presents $\rho \geq 0.36$ e Å^{-3} (Ref. 21) (Fig. 1 and Table 2). Furthermore, the large ellipticity parameters for critical points *a* and *b* in (*R*,*R*)-**1** (1.865 and 3.752, respectively) (Table 2) are indicative of a minor interaction.[23]

***N,N′*-Bis[(*R*)-1-phenylethyl]urea, (*R*,*R*)-2.** Relative to cyclic urea (*R*,*R*)-**1** (see above), the conformational behavior of the acyclic urea (*R*)-**2** is much more complex since rotation around the amidic segments leads to various possible arrangements of the 1-phenylethyl group in combination with *E* and *Z* conformations (see, for example, Ref. 24). An *ab initio* DFT (B3LYP/6–31G* level) evaluation of all rotamers originating from rotation around the N—C(O) and N—C(H) bonds afforded the seven energy minima ($E < 5.0$ kcal mol^{-1}), which are given in Table 3. This table does not include conformer *EEa*, whose energy was estimated to be >12.0 kcal mol^{-1}.

It can be appreciated from Table 3 that the two conformers of lowest energy, i.e. *EZa* and *ZZa* ($E_{rel} = 0.0$ 0.0 and 0.2 kcal mol^{-1}, respectively), fulfil expectations in terms of the concept of allylic $A^{1,3}$ strain. Indeed, the C—H bonds in these conformers are oriented in a

Table 3. Relative energies for the conformers of lowest energy of (*R*,*R*)-**2**, according to *ab initio* DFT B3LYP/6–31G* calculations



Conformer	Total energy (hartree)	$E_{rel.}$ (kcal mol^{-1})	Dihedral H—C*—N—C(O) angles (°)
ZZa	−844.272822	0.22	−24.6 and −24.6
ZZb	−844.268623	2.86	−13.4 and −167.5
ZZc	−844.266308	4.31	166.7 and −166.7
EZa	−844.273178	0.00	−26.4 and −38.4
EZb	−844.268699	2.81	39.8 and 173.4
EZc	−844.26946	2.33	164.0 and −39.5
EZd	−844.265698	4.69	167.7 and 171.6

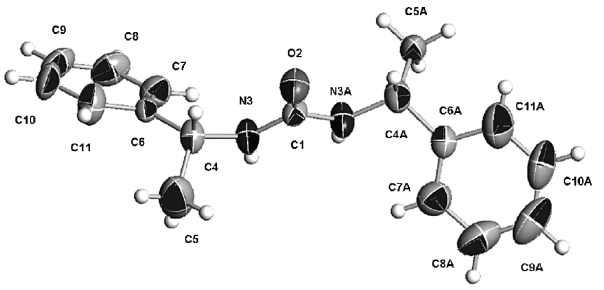


Figure 2. X-ray crystallographic structure and solid-state conformation of *N*,*N*′-bis[(*R*)-1-phenylethyl]urea, (*R*,*R*)-**2**

syn-periplanar manner to the N—C(O) segment. In the rest of the isomers, allylic $A^{1,3}$ strain induced by the methyl and phenyl substituents results in higher energy content (lower stability).

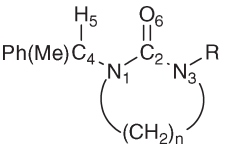
Figure 2 presents the x-ray crystallographic structure and the solid-state conformation of (*R*,*R*)-**2**. The structure was solved and refined using SHELX-97,[25a] within WinGX program version 1.64.05.28.[25b] Crystal data: $C_{17}H_{20}N_2O_1$, molecular weight = 268.35, orthorhombic $P2\ 2_1\ 2_1$, $a = 4.6697(2)$ Å, $b = 9.8125(4)$ Å, $c = 16.3979(7)$ Å, $\alpha = 90.0°$, $\beta = 90.0°$, $\gamma = 90.0°$, $V = 751.38(5)$ Å^3, crystal size $0.17 \times 0.30 \times 0.48$ mm^3, $R1 = 0.0401$ ($wR2 = 0.0982$). [Atomic coordinates for the structures reported in this paper have been deposited at the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 IEZ, UK (Fax +44 1223 336036; E-mail: deposit@ccdc.cam.ac.uk; deposition number CCDC 263119.] The C—H bonds at the *N*-1-phenylethyl groups orient themselves in a *syn*-periplanar manner relative to the N═C═O segment. Therefore, as a consequence of allylic $A^{1,3}$ strain, the molecule adopts a quasi-C_2 arrangement in the crystal.

***N*,*N*′-Bis[(*S*)-1-phenylethyl]propyleneurea, (*S*,*S*-3.** This chiral urea was modeled at the B3LYP/6–31G* level. The optimized structure (Table 4) presents a half-chair ring conformation with the carbonyl group oriented along the C_2 symmetry axis. The calculated energy difference between conformers **I** and **J** [Eqn (4)] is 1.27 kcal mol^{-1}, the former being more stable.

(4)

Again, in conformer **I** [*syn*-periplanar arrangement between the C—H bond and the N—C(O) segment] allylic $A^{1,3}$ strain is minimized. Nevertheless, it can be appreciated that $\Delta E(\mathbf{I} \rightleftharpoons \mathbf{J}) = 1.27$ kcal mol^{-1} in (*S*,*S*)-**3** is significantly lower than $\Delta E(\mathbf{A} \rightleftharpoons \mathbf{B}) = 2.35$ kcal mol^{-1} calculated for six-membered (*R*,*R*)-**1** at the same level of theory. This difference in conformational bias can easily be accounted for in terms of the structural differences in the five- and six-membered rings. In particular, the interatomic distance between the carbonyl oxygen and the C—H hydrogen of interest are estimated as 2.15 Å in (*R*,*R*)-**1** and 2.39 Å in (*S*,*S*)-**3**. Hence, manifestation of the allylic $A^{1,3}$ strain effect is more evident in the former system.

Table 4. Optimized geometry of lowest energy in (*R*,*R*)-**1**, (*R*,*R*)-**2**, (*S*,*S*)-**3** and (*R*)-**6** at the B3LYP/6–31G* level (distances in Å, angles in degrees; the phenyl ring is not included).



(*R*,*R*)-**1**, R = Ph(Me)CH, n = 3
(*R*,*R*)-**2**, R = Ph(Me)CH, n = 0
(*S*,*S*)-**3**, R = Ph(Me)CH, n = 2
(*R*)-**6**, R = H, n = 3

	(*R*,*R*)-**1**	(*R*,*R*)-**2**	(*S*,*S*)-**3**	(*R*)-**6**
N_1—C_2	1.385	1.378	1.387	1.387
C_2—N_3	1.385	1.391	1.387	1.381
N_1—C_4	1.478	1.472	1.470	1.478
C_4—H_5	1.091	1.092	1.094	1.092
C_2—O_6	1.238	1.230	1.228	1.232
N_1—C_2—N_3	117.3	115.3	108.0	116.5
N_1—C_4—H_5	104.0	104.4	103.5	103.6
N_1—C_2—O_6	121.3	123.8	126.0	123.2
N_3—C_2—O_6	121.4	120.9	126.0	120.3
H_5—C_4—N_1—C_2	7.6	−26.4	−26.6	−12.7
C_4—N_1—C_2—O_6	1.3	8.7	1.3	5.6
C_4—N_1—C_2—N_3	−179.6	−168.9	162.2	−177.3

Recrystallization of (*S*,*S*)-**3** afforded single crystals suitable for x-ray analysis (Fig. 3). The structure was solved and refined using SHELX-97,[25a] within WinGX program version 1.64.05.28.[25b] Crystal data: $C_{19}H_{22}N_2O_1$, molecular weight = 294.39, orthorhombic $P2_12_12_1$, $a = 8.6014(3)$ Å, $b = 12.1590(4)$ Å, $c = 15.8840(6)$ Å, $\alpha = 90.0°$, $\beta = 90.0°$, $\gamma = 90.0°$, $V = 1661.22(10)$ Å^3, crystal size $0.30 \times 0.37 \times 0.40$ mm^3, $R1 = 0.0394$ ($wR2 = 0.0846$) (deposition number CCDC 263120). Most interesting is the propeller-like orientation

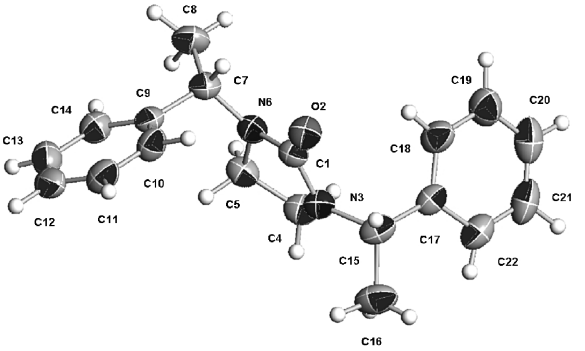


Figure 3. X-ray crystallographic structure and solid-state conformation of *N*,*N*′-bis[(*S*)-1-phenylethyl]ethyleneurea, (*S*,*S*)-**3**

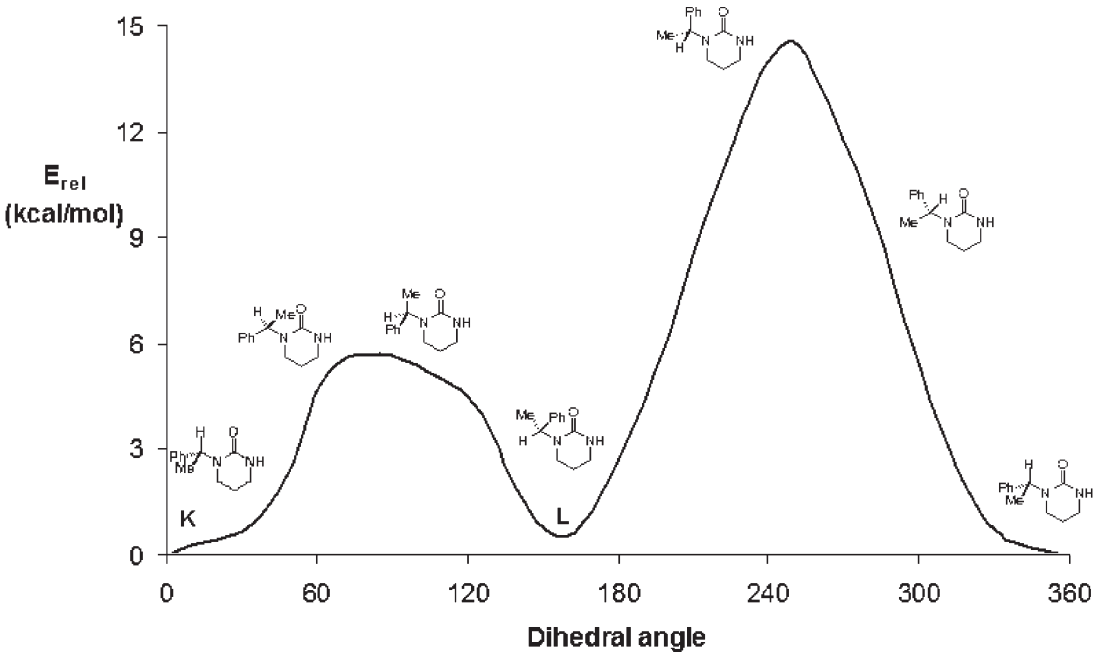


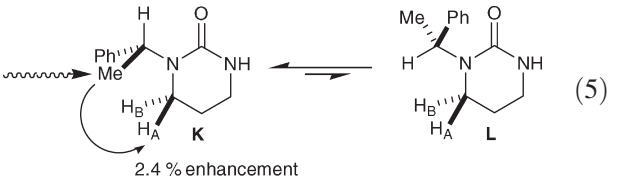
Figure 4. Rotation around the N—C* bond in (*R*)-**6**, according to HF/3–21G* calculations (fully optimized geometries)

of the 1-phenylethyl groups, which are expected to lead to high enantioselectivities in reactions taking place with a suitable substrate coordinated to the C═O oxygen atom. Again, the solid-state structure of (*S*,*S*)-**3** fulfils expectation based on the concept of allylic $A^{1,3}$ strain.

***N*-[(*R*)-1-Phenylethyl]propyleneurea, (*R*)-6.** The potential energy surface (PES) presented in Fig. 4 was obtained by constraining the H—C—N—C(O) dihedral angle for rotation about the C—N bond and fully optimizing (B3LYP/6–31G* level) the remaining internal coordinates. Intervals of 10 ° were used.

As seen in Fig. 2, the two lowest energy rotamers present H—C—N—C(O) dihedral angles of 0 ° and 195 °, the former being 2.04 kcal mol^{-1} more stable. Once again, this observation is in agreement with expectation in terms of minimization of allylic $A^{1,3}$ strain.

Support for this conclusion was acquired experimentally by means of ^{1}H NMR spectroscopy, and in particular from observation of a significant nuclear Overhauser effect (NOE) on one of the diastereotopic[26] hydrogens adjacent to the *N*-1-phenylethyl group. As illustrated in Eqn (5), a 2.4% enhancement at H_A upon irradiation of the methyl group is congruent with a predominance of conformer **K** and a dihedral angle $\tau = 0\,°$.



(5)

Summary

Theoretical analysis by means of semiempirical (AM1 and PM3) and *ab initio* (HF and DFT) methods confirm the predominance of those conformations that minimize allylic $A^{1,3}$ strain in *N*-(1-phenylethyl)-containing ureas **1**–**3** and **6**. This conformational bias suggests that chiral ureas such as **1**–**3** and **6** or their derivatives should be effective promoters of stereoselective reactions,[27] owing to the substantial steric and electronic differences presented by the hydrogen, methyl and phenyl groups in the 1-phenylethyl chiral auxiliary.

EXPERIMENTAL

General methods

TLC: silica gel F_{254} plates; detection with UV radiation or iodine vapor. Flash column chromatography:[28] silica gel (230–400 mesh). Melting-points: not corrected. ^{1}H NMR spectra: 60, 270 and 400 MHz spectrometers. ^{13}C NMR spectra: 22.5, 67.8, and 100 MHz spectrometers. Chemical shifts (δ) in ppm downfield from internal TMS reference; the coupling constants (J) are given in Hz. Optical rotations were measured in a polarimeter, using the sodium D-line (589 nm). Mass spectra: 20 eV.

Computational methods

Geometry optimizations (with no symmetry constraints) of all conformers were performed using semiempirical

(PM3 and AM1) and *ab initio* (HF and B3LYP) methods, using the Gaussian 98, Revision A.7,[29] series of programs. Thermodynamic corrections of energy in *ab initio* calculations were carried out by zero-point energy (ZPE) correction. The consideration of electronic correlation is very important in conformational studies;[30] thus, hybrid functionals B3LYP at the 6–31G(d,p) or 6–31G(d) level and also *ab initio* level were examined.

Topological analysis of (*R*,*R*)-**1** was possible by means of AIM2000[22] (atoms in molecules package), a set of programs that defines the properties of atoms and bonding patterns [charge density (ρ), Laplacians ($\nabla^2\rho$) and ellipticities (ε) of critical points between atoms] in a molecule.

Syntheses

N,N′-Bis[(R)-1-phenylethyl]propyleneurea, (R,R)-**1**. This compound was prepared according to the procedure developed in our laboratory.[12]

N,*N*′-Bis[(*R*)-1-phenylethyl]urea, (*R*,*R*)-**2**. The procedure described in the literature[15] was followed. The crude product was purified by silica gel flash chromatography[28] (CH_2Cl_2–AcOEt, 8:2) to give a white solid (79% yield), m.p. 209–210 °C (lit.[31] m.p. 207–209 °C). $[\alpha]_D^{25\,°C} = +55.6$ ($c = 0.85$, EtOH) {lit.[31] $[\alpha]_D^{25\,°C} = +51.7$ (EtOH, concentration not given)}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.26 (d, $J = 7.0$ Hz, 6H), 4.69 (dq, $J^1 = 8.0$ Hz, $J^2 = 7.0$ Hz, 2H), 6.25 (d, $J = 8.0$ Hz, 2H), 7.16–7.32 (m, 10H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.9, 40.6, 126.2, 126.9, 128.7, 146.2, 157.0.

N,*N*′-Bis[(*S*)-1-phenylethyl]ethyleneurea, (*S*,*S*)-**3**. In a 250 ml round-bottomed flask provided with a magnetic stirrer was placed 5.37 g (20.0 mmol) of *N*,*N*′-bis[(*S*)-1-phenylethyl]ethane-1,2-diamine[16] dissolved in 100 ml of dichloromethane. The solution was cooled to 0 °C before the dropwise addition of 2.11 g (7.1 mmol) of triphosgene dissolved in 50 ml of dichloromethane. The ice–water bath was removed and stirring was continued for 24 h. Isolation of the product involved addition of 50 ml of 1.0 M HCl. The aqueous phase was separated and washed with 50 ml of dichloromethane and the combined organic layers were dried and concentrated in a rotary evaporator. The crude product was purified by flash chromatography[28] (hexane–EtOAc, 9:1) to give 2.36 g (40% yield) of (*S*,*S*)-**3** as white crystals, m.p. 73–74 °C. $[\alpha]_D^{25\,°C} = -84.4$ ($c = 2.2$, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.49 (d, $J = 7.1$ Hz, 6H), 2.86 (m, 2H), 3.17 (m, 2H), 5.32 (q, $J = 7.1$ Hz, 2H), 7.24–7.35 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.3, 37.7, 50.3, 127.2, 127.3, 128.4, 140.9, 160.1. MS: *m/z* 294 (M^+, 53), 280 (14), 189 (42), 175 (45), 105 (100). Anal. calcd for $C_{19}H_{22}N_2O$: C, 77.51; H, 7.53. Found: C, 77.59; H, 7.75%.

3-[(R)-1-Phenylethylamino]propionitrile, (R)-**4**. In a 125 ml round-bottomed flask provided with a magnetic stirrer was placed 11.0 g (90.9 mmol) of (*R*)-1-phenylethylamine dissolved in 60 ml of methanol. To this solution was added 6.95 ml (100 mmol) of acrylonitrile and the resulting mixture was heated at reflux for 18 h. Concentration in a rotary evaporator afforded the crude product that was distilled in a Kugelrohr at 110–113 °C/0.1 mmHg to give 14.9 g (95% yield) of (*R*)-**4**, $[\alpha]_D^{25\,°C} = +69.9$ ($c = 1.55$, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.37 (d, $J = 6.6$ Hz, 3H), 1.55 (bs, 1H), 2.31–2.49 (m, 2H), 2.69–2.84 (m, 2H), 3.81 (q, $J = 6.6$, 1H), 7.24–7.37 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 18.9, 24.5, 42.9, 57.8, 118.8, 126.5, 127.3, 128.6, 144.8. MS: *m/z* 174 (M^+, 1), 160 (12), 159 (100), 105 (41), 91 (10).

N-[(*R*)-1-Phenylethyl]propylene-1,3-diamine, (*R*)-**5**. In a hydrogenation flask were placed 3.33 g (19.1 mmol) of (*R*)-**4** and 0.33 g of 5% rhodium on alumina before the addition of 60 ml of methanol saturated with ammonia. The flask was pressurized to 500 psi of hydrogen and shaken at ambient temperature for 18 h. The reaction mixture was filtered over Celite, concentrated and the crude product was purified by distillation in a Kugelrohr, b.p. 100–105 °C/1.0 mmHg, to afford 3.06 g (90% yield) of (*R*)-**5** as a colorless liquid, $[\alpha]_D^{25\,°C} = +53.0°$ ($c = 1.86$, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.34 (d, $J = 6.6$ Hz, 3H), 1.59 ($\sim$q, $J = 6.8$ Hz, 2H), 2.06 (br, 3H), 2.40–2.59 (m, 2H), 2.72 ($\sim$t, $J = 6.8$, 2H); 3.73 (q, $J = 6.6$, 1H), 7.21–7.32 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.5, 34.0, 40.6, 45.7, 58.5, 126.9, 127.2, 128.8, 145.8. MS: *m/z* 179 ($M^+ + 1$, 5), 120 (100), 105 (94), 91 (34), 73 (60). HRMS (FAB): calcd for $C_{11}H_{19}N_2$ ($M^+ + H$): 179.1548. Found: 179.1541.

N-[(*R*)-1-Phenylethyl]propyleneurea, (*R*)-**6**. In a 150 ml round-bottomed flask provided with a magnetic stirrer were placed 2.3 g (12.8 mmol) of (*R*)-**5**, 3.6 ml (26.1 mmol) of triethylamine and 8.0 ml of dichloromethane. The resulting solution was cooled to 0 °C before the dropwise addition of 1.3 g (4.5 mmol) of triphosgene dissolved in 30 ml of dichloromethane. Stirring was continued for 30 min at 0 °C and for 2 days at ambient temperature. The reaction mixture was treated with 50 ml of 1.0 M HCl and the organic phase was separated, washed with brine solution, dried and concentrated to give the crude product, which was purified by flash cromatography[28] with EtOAc as eluent. (*R*)-**6** was obtained (2.05 g, 78% yield) as white crystals, m.p. 94–96 °C $[\alpha]_D^{25\,°C} = +99.2°$ ($c = 1$, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.50 (d, $J = 7.0$ Hz, 3H), 1.78 (m, 2H), 2.79 (m, 1H), 3.08 (m, 1H), 3.27 (m, 2H), 5.28 (bs, 1H), 5.89 (q, $J = 7.0$ Hz, 1H), 7.21–7.36 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 15.8, 22.3, 39.3, 40.5, 50.6, 127.0, 127.4, 128.4, 141.5, 156.5. MS: *m/z* 205 ($M^+ + 1$, 17), 204 (M^+, 100), 189 (87), 161 (24), 127 (16), 105

(21). Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.70. Found: C, 70.45; H, 8.11; N, 13.78%

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