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N,N′-Bis[(*R*)-2-hydroxy-2-phenylethyl]-*N,N′*-bis[(*S*)-1-phenylethyl]pyridine-2,6-dicarboxamide: stabilization of an asymmetric conformer through the formation of a double intramolecular hydrogen bond

Martha Sosa-Rivadeneyra,[a] Leticia Quintero,[a] Cecilia Anaya de Parrodi,[b] Eusebio Juaristi[c] and Sylvain Bernès[d]*

[a]Centro de Investigación de la Facultad de Ciencias Químicas, Universidad Autónoma de Puebla, AP 1607, 72001 Puebla, Pue., Mexico, [b]Departamento de Química y Biología, Universidad de las Américas, Santa Catarina Mártir, Cholula, 72820 Puebla, Pue., Mexico, [c]Departamento de Química, Centro de Investigación y de Estudios Avanzados, Instituto Politécnico Nacional, 07000 México, DF, Mexico, and [d]Centro de Química, Instituto de Ciencias, Universidad Autónoma de Puebla, AP 1613, 72000 Puebla, Pue., Mexico

Correspondence e-mail: sylvain_bernes@hotmail.com

Key indicators

Single-crystal X-ray study
T = 299 K
Mean σ(C–C) = 0.004 Å
R factor = 0.036
wR factor = 0.097
Data-to-parameter ratio = 11.0

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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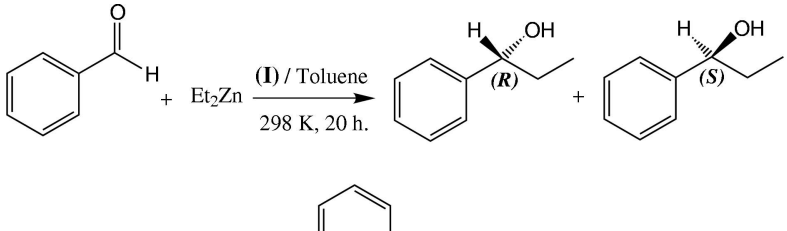
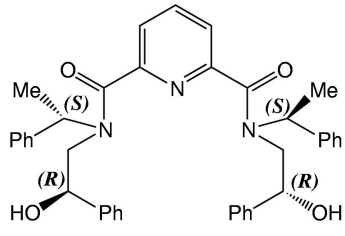
The title compound, $C_{39}H_{39}N_3O_4$, although having potential C_2 molecular symmetry, crystallizes as an asymmetric conformer, due to a couple of strong intramolecular hydrogen bonds involving hydroxyl groups and a pyridine N atom. This geometrical feature explains why this compound behaves as a poor chiral inductor for asymmetric synthesis.

Comment

Chiral N-containing compounds with C_2 molecular symmetry (Whitesell, 1989), such as amines, amides and pyridine derivatives, have been shown to be useful chiral inductors for asymmetric synthesis. They have been used as efficient auxiliaries for the addition of diethylzinc to benzaldehyde (Williams & Fromhold, 1997; Kwong & Lee, 1999; Pastor & Adolfsson, 2002; Sosa-Rivadeneyra *et al.*, 2003; Cobb & Marson, 2005), asymmetric allylic substitution (Hwang *et al.*, 1998), stereocontrolled addition of trimethylsilyl cyanide (Rassias *et al.*, 2000) and enantioselective conjugated addition of diethylzinc to chalcone (Bolm *et al.*, 1992), among other reactions. In this context, we searched for new C_2 chiral molecules incorporating an (*S*)-1-phenylethylamine moiety. We prepared the title compound, (I), by condensation of pyridine-2,6-dicarbonyl dichloride with (1*R*,1′S)-2-{[*N*-(1′-phenylethyl)]amino}-1-phenylethanol (Alcaide *et al.*, 1981; Anaya de Parrodi *et al.*, 1996). However, trials for enantioselective alkylation of benzaldehyde with diethylzinc (see scheme below) revealed that (I) only induces a moderate enantiomeric enhancement (20% e.e., 1*R*). In the same way, a poor e.e. was observed when using (I) as auxiliary during the asymmetric synthesis of 1,3-diphenylpentan-1-one from chalcone (14% e.e., 3*R*).





(I)

An extensive variable-temperature two-dimensional-NMR study of (I) showed that two conformers co-exist in solution

through an equilibrium between the *Z* and *E* conformations of the *N*-substituted amide groups, involving a slow rotation around the σ N—(C═O) bonds. Thus, one conformer retains the C_2 symmetry, while the other belongs to point group C_1. The asymmetric C_1 conformer is strongly favored in solution, the C_1:C_2 ratio being 8:1 at 298 K, as determined from a dynamic NMR study (Sosa-Rivadeneyra, 2003). Because of the steric hindrance of phenylethyl and hydroxyphenylethyl groups bonded to the N atoms, the activation energy for interconversion between the C_1 and C_2 forms is relatively high, *ca* 14 kcal mol^{-1}. Finally, an observation of great interest is that protons of the hydroxyl groups give ^{1}H NMR signals at significantly different chemical shifts, δ = 8.90 and 5.51 p.p.m., suggesting a participation of these functionalities in a hydrogen-bonding scheme. We have now completed this study with the X-ray crystal structure determination of (I), in order to establish which conformer is stabilized in the solid state, as well as how the hydrogen-bonding scheme determines the solid-state conformation.

The asymmetric unit of (I) contains one molecule in a general position, with no indication of non-crystallographic symmetry, showing that the C_1 conformer is stabilized in the solid state (Fig. 1). The approximate C_2 axis is retained for the pyridine core and for the carbonyl substituents at C2 and C6, as reflected by similar torsion angles N1—C2—C23—O24 = 125.6 (2)° and N1—C6—C7—O8 = 132.7 (2)°. Amide N atoms also conform to this symmetry, with angles N1—C2—C23—N25 = −49.3 (2)° and N1—C6—C7—N9 = −43.1 (3)°. The C_2 symmetry is definitively broken for the other substituents bonded to amine N atoms N9 and N25. Thus, non-C_2-related positions are found for hydroxyphenylethyl and phenylethyl groups. For instance, the C2—C23—N25—C32 and C6—C7—N9—C16 angles are 170.88 (15) and −26.0 (3)°, respectively (Table 1).

Hydroxyl groups O18 and O34 generate an intramolecular hydrogen-bonding scheme (Fig. 1 and Table 2), which is also consistent with the C_1 symmetry. Functional group O18—H18 acts as both a single hydrogen-bond donor (with pyridine atom N1 as acceptor) and acceptor (with the O34—H34 hydroxyl group as donor). This double intramolecular hydrogen bond gives rise to fused *S*(8) and *S*(10) motifs and a large *S*(14) motif. The two hydrogen bonds have different natures but display very similar geometries, which correspond to strong interactions. Thus, the main conformer observed for (I) in solution is most probably that retained in the solid state. As a whole, solution and solid-state data clearly explain why (I) is a disappointing chiral auxiliary for asymmetric synthesis: the main conformer in solution being asymmetric, the number of possible competing diastereomeric transition states during the reaction increases, producing a decrease in the asymmetric induction (Whitesell, 1989). On the other hand, steric hindrance of the phenyl rings and arrangement of the hydroxyl groups make the N atoms in (I) inaccessible for a transition metal.

Interestingly, an isographic intramolecular hydrogen-bonding scheme was described previously for a podand related to (I), namely 2,6-bis[(2-hydroxyphenoxy)methyl]-pyridine (Habata *et al.*, 2002). However, in this case, hydrogen bonds are of questionable significance, with O—H···O and O—H···N angles ranging from 72 to 144°. As a consequence, this podand is able to complex alkali metals, as demonstrated by alkali metal affinity studies in the gas phase and crystallization of a sodium adduct from an acetonitrile solution.

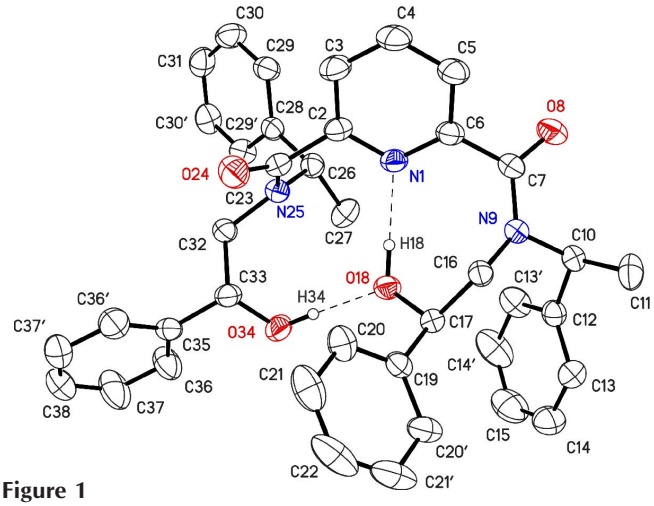


Figure 1
The structure of (I), with displacement ellipsoids drawn at the 30% probability level. Intramolecular hydrogen bonds are shown as dashed lines. For the sake of clarity, H atoms not involved in the hydrogen-bonding scheme have been omitted.

Experimental

A mixture of dipicolinic acid (0.200 g, 1.196 mmol) and thionyl chloride (3 ml) was refluxed for 3 h. Unreacted thionyl chloride was removed by evaporation under reduced pressure, affording 2,6-pyridinedicarbonyl dichloride. Separately, (1*R*,1′*S*)-2-{[*N*-(1′-phenylethyl)]amino}-1-phenylethanol (0.576 g, 2.39 mmol) was dissolved in dry CH_2Cl_2 (15 ml) and added to freshly distilled Et_3N (0.484 g, 4.78 mmol). After 30 min under agitation at 298 K, the previously prepared 2,6-pyridinedicarbonyl dichloride was added with continued agitation and allowed to react for 15 h at 298 K. The mixture was then quenched with $NaHCO_3$ and the organic phase extracted with CH_2Cl_2. Evaporation of the solvent afforded (I) as a crystalline solid in a 60% yield {m.p. 475–477 K; $[\alpha]_D$ = −321.4° (*c* = 2.1 g per 100 ml, $CHCl_3$)}.

Crystal data

$C_{39}H_{39}N_3O_4$
M_r = 613.73
Monoclinic, $P2_1$
a = 9.7976 (9) Å
b = 14.3385 (13) Å
c = 11.9807 (10) Å
β = 94.534 (4)°
V = 1677.8 (3) Å^3
Z = 2
D_x = 1.215 Mg m^{-3}
Mo *K*α radiation
Cell parameters from 49 reflections
θ = 4.4–13.5°
μ = 0.08 mm^{-1}
T = 299 (1) K
Prism, colorless
0.6 × 0.6 × 0.6 mm

Data collection

Bruker *P*4 diffractometer
$2\theta/\omega$ scans
Absorption correction: none
7926 measured reflections
4642 independent reflections
3939 reflections with $I > 2\sigma(I)$
R_{int} = 0.017
θ_{max} = 29.0°
h = −13 → 6
k = −1 → 19
l = −16 → 16
3 standard reflections
every 97 reflections
intensity decay: 1%

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0436P)^2 + 0.1246P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.036$	$(\Delta/\sigma)_{max} < 0.001$
$wR(F^2) = 0.097$	$\Delta\rho_{max} = 0.13$ e Å^{-3}
$S = 1.02$	$\Delta\rho_{min} = -0.10$ e Å^{-3}
4642 reflections	Extinction correction: *SHELXTL-Plus*
422 parameters	Extinction coefficient: 0.0140 (16)
H atoms treated by a mixture of independent and constrained refinement	

Table 1
Selected geometric parameters (Å, °).

N1—C2	1.345 (2)	C23—O24	1.227 (3)
N1—C6	1.341 (2)	C23—N25	1.358 (3)
C7—O8	1.223 (3)	N25—C26	1.489 (3)
C7—N9	1.355 (2)	N25—C32	1.472 (2)
N9—C10	1.485 (2)	C33—O34	1.414 (2)
N9—C16	1.468 (2)	O18—H18	0.91 (3)
C17—O18	1.414 (2)	O34—H34	0.89 (3)
C6—N1—C2	118.54 (15)	O24—C23—N25	122.73 (18)
O8—C7—N9	123.13 (19)	O24—C23—C2	117.86 (19)
O8—C7—C6	116.94 (17)	N25—C23—C2	119.20 (17)
N9—C7—C6	119.79 (17)	C23—N25—C26	122.52 (15)
C7—N9—C10	116.40 (15)	C23—N25—C32	115.58 (17)
C7—N9—C16	122.86 (16)	C32—N25—C26	118.94 (15)
C16—N9—C10	117.93 (14)	O34—C33—C32	111.26 (18)
O18—C17—C16	111.95 (13)	O34—C33—C35	109.04 (15)
O18—C17—C19	111.27 (14)	C35—C33—C32	108.30 (15)
C19—C17—C16	109.00 (15)		
N1—C6—C7—O8	132.7 (2)	N1—C2—C23—N25	−49.3 (2)
N1—C6—C7—N9	−43.1 (3)	C2—C23—N25—C26	−28.8 (2)
C6—C7—N9—C10	173.40 (17)	C2—C23—N25—C32	170.88 (15)
C6—C7—N9—C16	−26.0 (3)	C23—N25—C26—C27	132.52 (19)
C7—N9—C10—C11	95.0 (2)	C23—N25—C32—C33	−75.4 (2)
C7—N9—C16—C17	117.74 (19)		
N1—C2—C23—O24	125.6 (2)		

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O18—H18···N1	0.91 (3)	1.82 (3)	2.7343 (19)	174 (3)
O34—H34···O18	0.89 (3)	1.84 (4)	2.7300 (19)	177 (3)

In the absence of significant anomalous scattering effects, Friedel pairs were merged. The absolute configuration for the chiral centers was determined as *S*-C10, *R*-C17, *S*-C26, *R*-C33, assuming that the configuration of the chiral starting material was unchanged during the synthesis. H atoms of the hydroxyl groups, H18 and H34, were found in a difference map and refined, with $U_{iso}(H) = 1.5U_{eq}(O)$. Other H atoms were placed in idealized positions with C—H distances of 0.93 Å for aromatic CH, 0.96 Å for methyl CH_3, 0.97 Å for methylene CH_2 and 0.98 Å for methine CH, and refined using a riding model, with $U_{iso}(H) = 1.2U_{eq}(C)$ for aromatic CH, methine CH and methylene CH_2, and $1.5U_{eq}(C)$ for methyl CH_3.

Data collection: *XSCANS* (Siemens, 1996); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SHELXTL-Plus* (Sheldrick, 1998); program(s) used to refine structure: *SHELXTL-Plus*; molecular graphics: *SHELXTL-Plus*; software used to prepare material for publication: *SHELXTL-Plus*.

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