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The Origin of Atropisomerism in 2,2′-Bis((1*R*,2*R*,4*S*)-2-hydroxy-1,3,3-trimethylbicyclo[2.2.1]hept-2-yl)-1,1′-biphenyl: Synthesis, Structure and Energetics

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This article is dedicated to Prof. Paul von Ragué Schleyer on the occasion of his 70th birthday

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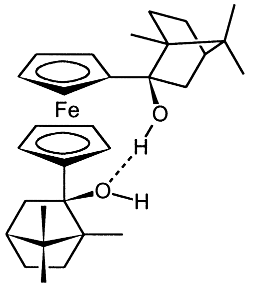
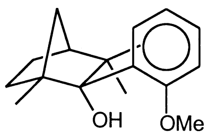
Abstract—In the X-ray crystal structure of 2,2′-bis((1*R*,2*R*,4*S*)-2-hydroxy-1,3,3-trimethylbicyclo[2.2.1]hept-2-yl)-1,1′-biphenyl (**3**-*R*) fenchyl alcohol units induce a *R*-sense of asymmetry at the biphenyl axis and support intramolecular hydrogen bonds between the hydroxy groups. Computational ONIOM evaluations of **3**-*R* and of its diastereomer with *S*-biphenyl axis (**3**-*S*) reveal a higher stability (>6 kcal/mol) for **3**-*R* and show how suitable alignments of 1,3,3-trimethylbicyclo[2.2.1]heptane units originate the observed *R*-biphenyl axis. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

Axially chiral biaryls play an eminent role in pharmacological natural products and as chiral ligands in asymmetric catalysis.[1] The stereochemical control of the biaryl axis is a challenging endeavor in the enantioselective synthesis of these compounds.[2] Chelating diols, e.g. TADDOLs[3] and BINOLs,[4] are frequently employed as chiral ligands and 2,2′-bis(hydroxymethyl)-1,1′-biphenyl derivatives have attracted much attention due to their ability to form clathrates with a variety of organic guest molecules.[5] Dimitrov et al. have reported the X-ray crystal structure of the chiral ferrocenyl diol **1**.[6] Intramolecular hydrogen bonding between the borneol moieties determine a gauche eclipsed alignment of the cyclopentadienyl moieties of the ferrocenediyl unit of **1**.

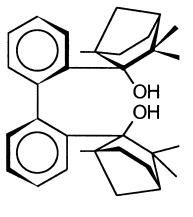


1

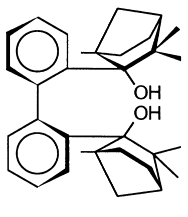


2

We have recently shown that chelating fenchyl alcohols (such as **2**) can be successfully employed as precatalysts in enantioselective diethylzinc additions to benzaldehyde.[7] Lithiated **2** also serves as 'chiral *n*-butyllithium trap'.[8] Is the fenchyl alcohol moiety capable of inducing and stabilizing asymmetry at the biaryl axis in biphenyl derivatives, e.g. in **3**?



3-*R*



3-*S*

Results and Discussion

To study the stereochemical influence of 2,2′-fenchyl alcohol units on the biaryl axis, we synthesized 2,2′-bis-((1*R*,2*R*,4*S*)-2-hydroxy-1,3,3-trimethylbicyclo[2.2.1]hept-2-yl)-1,1′-biphenyl **3** by addition of 2,2′-dilithiobiphenyl to (−)-fenchone. X-Ray crystal analysis of **3**[9] reveals the formation of intramolecular hydrogen bonds (O–H–OH: 2.2 Å, O–O: 3.0 Å, Fig. 1) between the hydroxy groups.[10] The dihedral angle of the biphenyl axis between 2- and 2′-carbon atoms is −95°. An *R*-sense of asymmetry is found at the biphenyl axis in the X-ray crystal structure of **3** (**3**-*R*) (Fig. 1).

Keywords: biaryls; asymmetric induction; bicyclic aliphatic compounds; computer-assisted methods.

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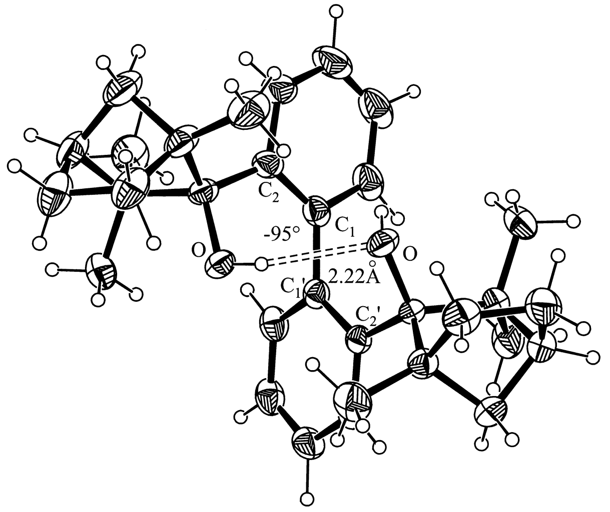
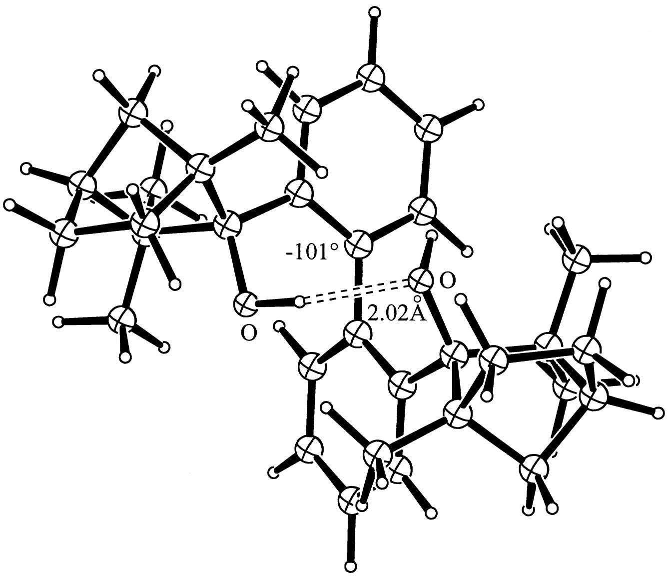


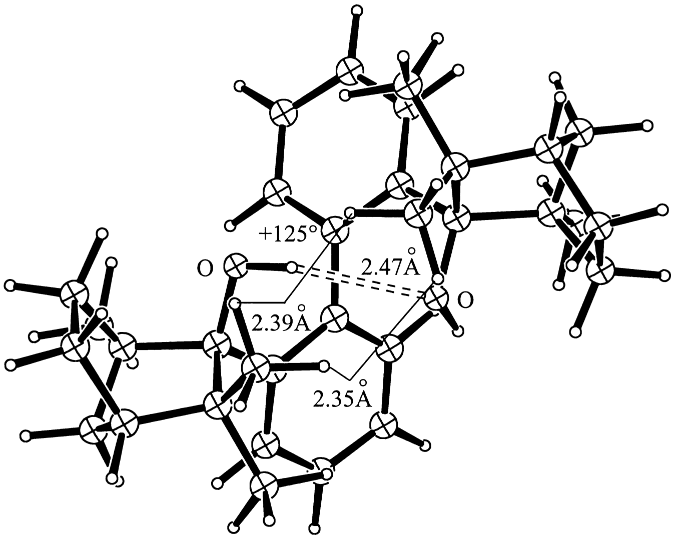
Figure 1. X-Ray crystal structure of **3**-*R*.

To explore the origin of atropisomerism in **3**-*S*, we computed gas phase structures of **3**-*R* and of **3**-*S*, which has a *S*-sense of asymmetry at the biphenyl axis (Table 1, Fig. 2).[11] As in the X-ray crystal structure of **3**-*R*, both computed structures **3**-*R* and **3**-*S* exhibit hydrogen bonding between the hydroxy functions (Table 2). The structure **3**-*S* is computed to be more than 6 kcal/mol less stable than **3**-*R* (Table 1). The lower stability of **3**-*S* is in agreement with the experimental formation of **3**-*R* (Fig. 1).

The destabilization of **3**-*S* relative to **3**-*R* (Table 1) arises from repulsion between methyl substituents of the bicycloheptane moieties (Table 2). While hydrogen bonding is established in the X-ray crystal structure and in computed **3**-*R* via the 'open sides' of the bicycloheptane units (Figs. 1 and 2), it proceeds in **3**-*S* close to the geminal methyl groups (Fig. 2). Hydrogen bonding forces in **3**-*S* unfavorable close contacts between C–H units (CH–HC: 2.35 Å), while no such close distances are apparent in experimental or



3-*R*



3-*S*

Figure 2. B3LYP/6-311++G**:AM1 ONIOM optimized structures.

Table 1. Computed absolute and relative energies of **3**-*R* and **3**-*S* (hydroxy functions were calculated by HF, MP2 or B3LYP methods, while AM1 was employed for the rest of the structures)

ONIOM-method[a]	**3**-*R* (C_1)	**3**-*S* (C_1)
HF/6-311++G**:AM1	−151.97787	−151.96807
$E_{rel.}$	0.0	+6.1
B3LYP/6-311++G**:AM1	−152.79148	−152.78109
$E_{rel.}$	0.0	+6.5
MP2/6-311++G**:AM1	−152.42343	−152.41334
$E_{rel.}$	0.0	+6.3

[a] Hydrogens were used as link atoms between the layers.

Table 2. Experimental (X-ray crystal structure) and computed (B3LYP/6-311++G**:AM1) geometries of **3**-*R* and **3**-*S* (hydroxy functions were computed by B3LYP, while AM1 was employed for the rest of the structures. Hydrogens were used as link atoms between the layers)

	3-*R* (X-ray)	**3**-*R* (comp.)	**3**-*S* (comp.)
O–H–O(H) (Å)	2.22	2.02	2.47
O–O (Å)	3.00	2.95	3.36
O–H–O (°)	153	159	153
$C_{(2)}$–C–C–$C_{(2')}$ (°)	−95	−101	+125
O–C–$C_{(2('))}$–$C_{(1('))}$ (°)	25, 31	21, 29	3, 5
CH–HC (Å)	3.50	3.13	2.35

computed **3**-*R* (Table 2). As a result, the distances between oxygens are significantly longer in **3**-*S* (O–O: 3.36 Å), relative to those in experimental and computed **3**-*R* (O–O: 3.00 and 2.95 Å, Table 2). This corresponds with a larger value of the dihedral angle between the biphenyl units in **3**-*S* (+125°) relative to the X-ray crystal structure and the computed structure of **3**-*R* (−95° and −101°, Table 2).

Conclusions

The asymmetry at the biphenyl axis in the X-ray crystal structure of **3**-*R* is induced and stabilized by favorable alignments of the bicycloheptane moieties, which also support hydrogen bonding between 2,2′-fenchyl alcohol units. The suitability of **3** as chiral ligand and as host to form clathrates with organic guest molecules is currently under investigation.

Experimental

All reactions were carried out under argon atmosphere using Schlenk-tube techniques. Solvents were dried by standard methods and distilled under argon prior to use.

Synthesis of 2,2′-bis((1*R*,2*R*,4*S*)-2-hydroxy-1,3,3-trimethylbicyclo[2.2.1]hept-2-yl)-1,1′-biphenyl 3. 2,2′-Dilithiobiphenyl (2 TMEDA) were synthesized by treating biphenyl with *n*-butyllithium/TMEDA for 2 h at 60°C.[12] To a suspension of 5 g (12.5 mmol) 2,2′-dilithiobiphenyl (2 TMEDA, M: 398.5) in hexanes 3.8 g (4.0 ml, 25 mmol) (−)-fenchone was added and the mixture was stirred at room temperature for 24 h. Hydrolytic work-up and recrystallization (two times) from diethylether yielded 4.3 g (9.4 mmol, 75%) of **3**. Analytic and spectroscopic data of **3**: mp: 242°C.; calcd: C 83.80, H 9.23, found C 83.79, H 9.25; ^{1}H NMR ($CDCl_3$, 300 MHz) 0.64 (3H, s), 0.69 (3H, s), 1.09 (3H, s), 1.15–2.41 (6H, m), 2.84 (1H, s), 6. 90 (1H, d), 7.09 (1H, t), 7.24 (1H, t) 7.59 (1H, d); ^{13}C NMR ($CDCl_3$, 75.5 MHz) 143.87, 141.00, 130.90, 129.71, 124.53, 124.13, 85.94, 54.49, 48.99, 46.28, 42.31, 33.83, 29.80, 23.48, 20.96, 17.32; $[\alpha]_D^{22}=-153$ (*c* 0.4, *n*-hexane); EI-MS: 458.3 (M^+), 440.3 (M^+-H_2O); IR (KBr, cm^{-1}) 3546 (sharp), 3437 (broad), 3113, 3047, 2932, 1593. X-Ray crystal data of **3**: $C_{32}H_{42}O_2$; $M=458.66$; space group *C*2; $a=23.1509(1)$ Å, $b=8.4984(1)$ Å, $c=20.713(1)$ Å, $\beta=102.529(1)$; $V=3978.11(5)$ Å^3; $Z=6$; $T=200(2)$ K; $\mu=0.069$ mm^{-1}; reflections total: 14 912, unique: 6590, observed: 4804 ($I>2\sigma(I)$); parameters refined: 604; $R1=0.0414$, $wR2=0.0880$; GOF=0.989 (crystallographic data have been deposited with the Cambridge Crystallographic Data Center).

Computational Section

All computed structures were fully optimized using Morokuma's ONIOM method implemented in GAUSSIAN98.[11] Ab initio (RHF/6-311++G**, MP2/6-311++G**) and hybrid DFT (B3LYP/6-311++G**) levels of theory were applied to the hydroxy groups, while the rest of the structures were computed by the semiempirical AM1 method. Hydrogen atoms were used as link atoms between the two layers. The structures were analyzed by frequency computations and showed no imaginary frequencies.

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9. Crystallographic data have been deposited with the Cambridge Crystallographic Data Center.

10. In the X-ray crystal structure of **3** one and a half molecules appear in the asymmetric unit. While both molecules of **3** exhibit similar geometries, the hydrogen atom in the H-bond of the half molecule is disordered. The given geometric values hence refer to the complete molecule in the asymmetric unit.

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