

# Atropisomerism of Cofacial Pyridine Rings. Synthesis, Proton NMR Spectra and Conformations of 1,8-Di(3'-pyridyl)naphthalene

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Restricted rotation,  $\pi$ -stacking, diastereomers, AM1 and PM3 computed geometries.

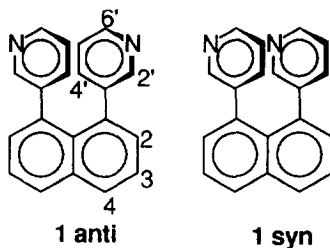
**Abstract:** The title compound prepared by Pd-catalyzed coupling of 1,8-dibromonaphthalene and diethyl(3-pyridyl)borane shows *syn-anti* diastereoisomerism due to restricted rotation at ambient temperatures. AM1 and PM3 computations indicate the preferred T-shaped transition state for rotation has a highly deformed naphthalene ring. There is a slight preference for H4' and not the nitrogen lone electron pair to be directed at the face of the other pyridyl ring. Copyright © 1996 Elsevier Science Ltd

Restricted rotation (atropisomerism) in cofacial arenes<sup>1-5</sup> and hetarenes<sup>6-9</sup> continues to command intense interest. Fascinating questions about barriers to rotation as well as unusual geometries due to extreme structural deformation associated with steric compression of stacked rings attract attention.

The most well known examples are 1,8-di(phenyl)naphthalenes, especially when at least one substituent such as a methyl group occupies an *ortho* position on a phenyl ring in order to increase barrier size.<sup>2,4</sup> Barriers to the interconversion of *syn* and *anti* diastereomers are largely related to ground state energies that reflect electrostatic through-space  $\pi$  interactions between the stacked rings.<sup>2,4,10,11</sup> Destabilizing interactions increase with the electron donating character of substituents.<sup>4,11</sup> Repulsion between the stacked rings is so severe that the rings bend away from each in order to increase their separation; the naphthalene ring is nonplanar.<sup>1,3,10</sup>

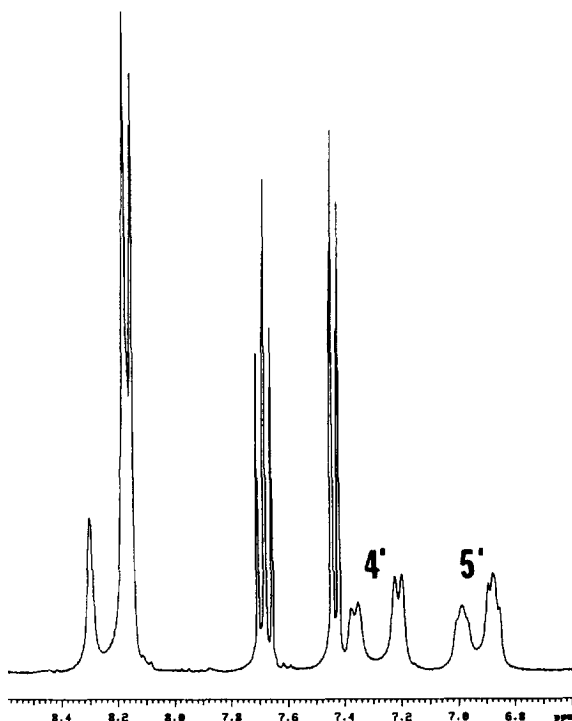
In contrast to the often laborious synthetic schemes used to prepare the diphenyl derivatives and the shorter Ullmann coupling, we report a simple and likely general synthesis of cofacial hetarenes based on a palladium-catalyzed crossed-coupling reaction. 1,8-Dibromonaphthalene<sup>7</sup> was coupled under Suzuki conditions<sup>12</sup> to diethyl(3-pyridyl)borane to give 1,8-di(3-pyridyl)naphthalene (**1**) (83%). 1,8-(2-Dithienyl)naphthalenes have been prepared from the thienyl Grignard reagent and the 1,8-diiodide in the presence of a Ni(II) catalyst; their NMR spectra are unexceptional.<sup>7</sup> Cofacial pyridines have been prepared by multistep syntheses using phenanthrene<sup>8</sup> and pentaphenes<sup>6</sup> as rigid platforms. Rotational barriers have been reported for 1,8-naphthalenes containing two 1,2,3-triazole rings.<sup>9</sup>

The remarkably simple proton NMR spectrum of **1** in DMSO-d<sub>6</sub> at 20 °C is shown in the Figure. The signals for the three types of naphthalene protons are sharp and well resolved. Pyridyl protons H4' and H5'

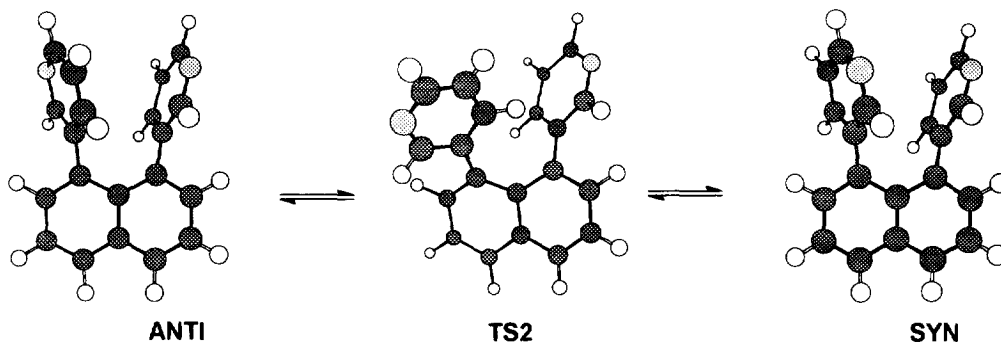


are highly shielded due to  $\pi$ -stacking interactions. By contrast, the pyridyl protons appear in two broadened sets representing *anti* (racemic,  $C_2$  axis) and *syn* (*meso*,  $\sigma$  plane) atropisomers in an approximate 1.4 to 1 ratio. A similar ratio is found for acetone solvent. But in  $CDCl_3$  at  $-20$  °C this ratio becomes 4.1 to 1. The coalescence temperature for the  $H5'$  protons of **1** in  $DMSO-d_6$  is about  $35$  °C, giving rise to a free energy of activation of approximately 15 kcal/mol, not unlike those values reported for simple arenes.<sup>3,4</sup>

The two possible T-shaped transition states for *syn-anti* interconversion place either the side with the two hydrogen atoms  $H4'$  and  $H5'$  of one ring toward the face of the other pyridyl ring or the side with hydrogen  $H2'$  and the lone electron pair on the nitrogen atom in the face of the second ring. AM1 and PM3 computations show that the former case describes the preferred geometry. Because the rings are splayed out from each other, essentially only  $H4'$  moves across the face of the second ring as shown in calculated structure 2TS. Moreover, the naphthalene ring also becomes distorted; the ring is twisted with the carbon atoms at the *peri* positions now located above and below the usual plane. The calculated activation enthalpies are 12.4



kcal/mol (AM1 and PM3) and 13.0 (AM1) and 12.8 (PM3) kcal/mol for the H-H and H-lone pair eclipsing transition states, respectively.



The less polar *anti* diastereomer is computed to be favored over the *syn* isomer by 0.6 kcal/mol (2.8 to 1) in the absence of solvent but only by about 0.3 kcal/mol (AM1) (1.7 to 1) and 0.2 kcal/mol (PM3) (1.4 to 1) in DMSO in reasonable agreement with our observations of 1.4 to 1 for DMSO solvent.

The magnetic anisotropy and electronic polarization caused by a nitrogen atom are likely to cause the large changes in chemical shifts of the pyridyl protons. These heteroatoms provide stereo and spectral differentiation, making the detection of diastereomers easy. Exocyclic groups as used in other substrates to provide chirality and barriers to rotation therefore are unnecessary.

Perhaps **1** is the structurally most simple 1,8-di(aryl)naphthalene to show clearly distinguishable *syn-anti* diastereomers at ambient temperatures.

## EXPERIMENTAL

**Computations:** All semiempirical computations were performed using AM1<sup>13</sup> and PM3<sup>14</sup> in conjunction with the VAMP program.<sup>15</sup> They were performed for isolated molecules in the gas phase as well as in DMSO where the solvent effect was approximated by the self consistent reaction field (SCRF) model. The pyridyl torsion angle was used as a reaction coordinate while optimizing all other geometrical parameters refined by gradient norm minimization and verified as transition states by force constant computations. Coordinate computations started from both the *syn* and *anti* minima.

**1,8-Di(3'-pyridyl)naphthalene: (1)** A mixture of 3.50 g (12.2 mmol) of 1,8-dibromonaphthalene,<sup>7</sup> 4.30 g (29.2 mmol) of diethyl(3-pyridyl)borane and 1.0 g (0.86 mmol) of Pd(PPh<sub>3</sub>)<sub>4</sub> in 100 mL of THF was degassed by bubbling nitrogen for 5 min. After adding a solution of 5.30 g (38.4 mmol) of K<sub>2</sub>CO<sub>3</sub> in 100 mL of degassed H<sub>2</sub>O the two-phase system was refluxed under nitrogen for 8 h. After cooling, the mixture

was diluted with 100 mL of  $\text{CHCl}_3$ . The organic layer was separated, dried ( $\text{MgSO}_4$ ) and concentrated under reduced pressure to a solid that was purified by flash chromatography on silica using methanol in ethyl acetate (15  $\rightarrow$  70%) to give 2.88 g (83%) of an off-white solid, mp 163-171  $^\circ\text{C}$ . Vacuum sublimation conveniently removed traces of Pd. Anal. Calcd. for  $\text{C}_{20}\text{H}_{14}\text{N}_2$ : C, 85.08; H, 5.00; N, 9.92. Found: C, 84.97, H, 5.05; N, 9.98.

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