Influence of the Position of an Annular Nitrogen Atom on the Magnitude of the Rotational Barriers in Atropisomers of 1,8-Dihetarylnaphthalenes

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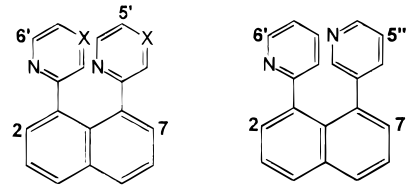
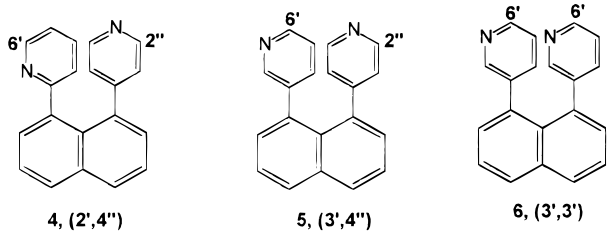
Five new atropisomerically chiral 1,8-dihetarylnaphthalenes were prepared by Pd(0)-catalyzed coupling reactions. Variable-temperature proton NMR spectra show those compounds with a 2′-pyridyl or 2′-pyrazinyl ring have a much lower energy barrier for rotation to interconvert conformational isomers than those with a 3′-pyridyl ring. Coalescence temperatures may differ by as much as 100 °C. The results of AM1 and PM3 computations indicate the preferred transition state for σ-bond rotation places the annular nitrogen atom in the 2′ or *ortho* position toward the face of the second hetaryl ring and not toward the naphthalene ring.

Stacked or cofacial heteroaromatic rings appear in a number of natural products, the most important being nucleic acids where the rings are offset to each other.[1] In 1,8-diaryl-[2−9] and 1,8-dihetarylnaphthalenes[10−13] the aromatic rings are π-stacked but constrained at the point of attachment to be within their van der Waals contact distance of 3.4 Å,[14,15] separations similar to those found in nucleic acids.[1] Dihetarylnaphthalenes provide a special model to study the interactions of aromatic rings not only in the ground state but also in the transition state for rotation where they adopt an approximate "T-shaped" edge-to-face conformation.

We report the synthesis of five new atropisomerically chiral, cofacial 1,8-dihetarylnaphthalenes, their variable-temperature proton NMR spectra, and the results of semiempirical computations. Our new data along with the results of our previous studies[11] show that the site of an unsubstituted annular nitrogen atom in the rotating hetaryl ring has a major influence on the magnitude of the energy barrier.

Three different kinds of cofacial systems were prepared by Pd-catalyzed cross-coupling reactions. Compounds **1** and **2** have two identical rings, 2′-pyridyl and 2′-pyrazinyl, respectively. They contain two chiral axes and can give rise to racemic (C_2 symmetry) and *meso* (plane of symmetry) conformational diastereomers. Other substrates with two different pyridyl rings possess either two stereogenic axes as in **3** where the pyridyl rings are bonded at the 2′ and 3″ positions or a single chiral axis as in **4** and **5** where the pyridyl rings are attached at their 2′ and 4″ or 3′ and 4″ positions, respectively, giving rise to conformational enantiomers. In **3**, both *anti* and *syn* conformational diastereomers are chiral. In **4** and **5**, the 4″ pyridyl ring is prochiral, having two protons at the α and β positions that are diastereotopic. We refer to these materials by number and more informatively by their site of attachment to the naphthalene ring; e.g., **1** becomes the 2′,2′ substrate. These compounds join the 3′,3′ isomer **6** we reported earlier.[11]





Results

All the cross-coupling reactions employed $Pd(PPh_3)_4$ as the catalyst. The source of the naphthalene ring usually was 1,8-dibromonaphthalene[10] (**7**) prepared from the 1,8-diamino compound.

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(1) Puglisi, J. D.; Wyatt, J. R.; Tinoco, I., Jr. *Acc. Chem. Res.* **1991**, *24*, 152.
(2) Cozzi, F.; Siegel, J. *Pure Appl. Chem.* **1995**, *67*, 683.
(3) Clough, R. L.; Roberts, J. D. *J. Am. Chem. Soc.* **1976**, *98*, 1018.
(4) House, H. O.; Campbell, W. J.; Gall, M. *J. Org. Chem.* **1970**, *35*, 1815.
(5) Cozzi, F.; Ponzini, F.; Annuziata, R.; Cinquini, M.; Siegel, J. S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1019.
(6) Cozzi, F.; Cinquini, M.; Annunziata, R.; Siegel, J. S. *J. Am. Chem. Soc.* **1993**, *115*, 5330.
(7) Cozzi, F.; Cinquini, M.; Annunziata, R.; Dwyer, T.; Siegel, J. *J. Am. Chem. Soc.* **1992**, *114*, 5729.
(8) Nugent, H. M.; Rosenblum, M. *J. Am. Chem. Soc.* **1993**, *115*, 3848.
(9) Cosmo, R.; Sternhell, S. *Aust. J. Chem.* **1987**, *40*, 1107.
(10) Kuroda, M.; Nakayama, J.; Hoshino, M.; Furusho, N.; Kawata, T.; Ohba, S. *Tetrahedron* **1993**, *49*, 3735.
(11) Zoltewicz, J. A.; Maier, N. M.; Fabian, W. M. F. *Tetrahedron* **1996**, *52*, 8703.
(12) Nagawa, Y.; Honda, K.; Nakanishi, H. *Magn. Reson. Chem.* **1996**, *34*, 78.
(13) Bahl, A.; Grahn, W.; Stadler, S.; Feiner, F.; Bourhill, G.; Bräuchle, C.; Reisner, A.; Jones, P. G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1485.
(14) Williams, V. E.; Lemieux, R. P.; Thatcher, G. R. J. *J. Org. Chem.* **1996**, *61*, 1927.
(15) Jorgensen, W. L.; Severance, D. L. *J. Am. Chem. Soc.* **1990**, *112*, 4768.

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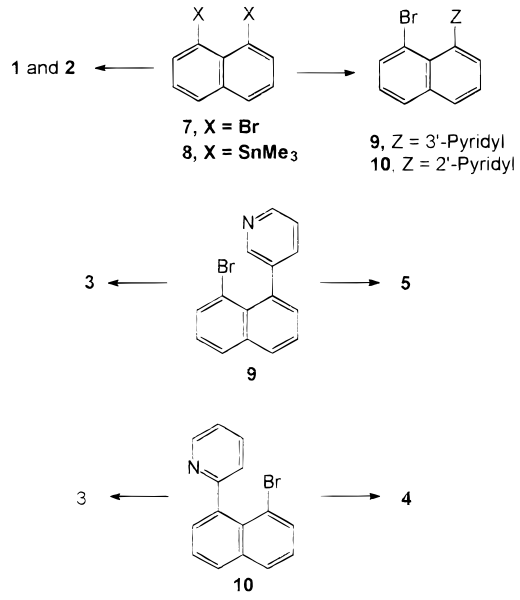


1,8-Di(2′-dipyridyl)naphthalene (1) and 1,8-Di(2′-dipyrazinyl)naphthalene (2). Two preparations of **1** made use of the so-called "reverse polarity" method in which the identity of the organometallic compound and the hetaryl halides were reversed. First, **7** was coupled with 2-(tributylstannyl)pyridine[16] in toluene (41%), and second, 1,8-bis(trimethylstannyl)naphthalene[17] (**8**) was joined to 2-brompyridine in DMF (28%) using Stille conditions for both.[18] 2-Chloropyrazine and **8** in DMF under similar conditions gave 32% of **2**.

Mixed Dipyridylnaphthalenes Derived from 1-Bromo-8-(3′-pyridyl)naphthalene (9). Diethyl(3-pyridyl)-borane was joined to dibromide **7** using aqueous carbonate and THF to give bromopyridine **9** (75%), which has been prepared by another coupling route.[13] When equimolar amounts of the starting materials were employed under Suzuki conditions,[13,19] just one coupling reaction took place and no difficulty was encountered with the formation of the bis-coupled product, which we easily prepared previously using excess borane.[11] Coupling of **9** with 2-(tributylstannyl)-[16] and 4-(tributylstannyl)pyridine[20] gave the constitutional isomers 2′-pyridyl-3″-pyridyl (**3**) (27%) and 3′-pyridyl-4″-pyridyl (**5**) (48%) derivatives, respectively.

Mixed Dipyridylnaphthalenes Prepared from 1-Bromo-8-(2′-pyridyl)naphthalene (10). The synthesis of **10** was not entirely satisfactory because some of the bis-coupled dipyridylnaphthalene was formed and column chromatography did not produce a clean separation with a high recovery. When **10** was coupled with diethyl(3-pyridyl)borane in water−THF and with 4-(tributylstannyl)pyridine[20] in DMF, the constitutional isomers 2′-pyridyl-3″-pyridyl **3** (64%) and 2′-pyridyl-4″-pyridyl-naphthalenes **4** (80%) were formed, respectively.

Variable Temperature Proton NMR Spectra at 300 MHz. The 2′,2′ compound at 20 °C in DMSO-d_6, $CDCl_3$, or acetone-d_6 gave sharp signals indicative of a rapidly equilibrating population-averaged *anti-syn* mixture of diastereomers appearing to be a single substance.

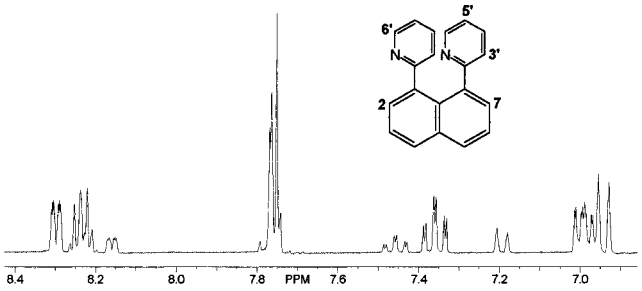


Figure 1. Proton NMR spectrum of 1,8-di(2′,2′-pyridyl)-naphthalene (**1**) in acetone-d_6 at −85 °C consisting of a mixture of *anti* and *syn* diastereomers in a 3.1:1 ratio. The low intensity peaks of the pyridyl ring at 8.16 (H6′), 7.45 (H4′), and 7.19 (H3′) ppm are associated with the minor *syn* diastereomer. The larger multiplets at 8.30 (H6′), 7.36 (H4′), and 6.93 (H3′) ppm are due to the *anti* form. The multiplet at 6.98 ppm comes from H5′ of both.

The spectrum of a $CDCl_3$ solution was especially revealing, showing seven well-separated signals for the seven different protons, all having integer area ratios; the multiplets were readily assigned by a COSY analysis. These observations stand in sharp contrast with those for our 3′,3′ isomer **6** that gave separate signals for the *anti-syn* diastereomers at ambient temperatures in the same solvents. The signals for the pyridyl rings of **6** were somewhat broadened, while those for the naphthalene remained sharp at 20 °C.[11]

Low-temperature studies on the 2′,2′ substrate using acetone-d_6 indicated that the rate of rotation about the pyridyl−naphthalene bond could be decreased to provide evidence for the presence of *anti-syn* diastereomers. At −55 °C, the pyridyl signals broadened; this appears to be a coalescence temperature for the 4′ triplets. At −65 °C separate signals for the two diastereomers were evident in a 3.3:1 ratio with the *anti* expected to be the major form. At −85 °C fine structure due to spin−spin splitting was present, Figure 1. This information allows the energy barriers for rotation to be estimated.

The rate constant at coalescence, k_c, is the sum of the rate constants for rotation of the pyridyl rings from the *anti* and *syn* ground states. This constant was estimated for the 2′,2′ material using a temperature of −55 °C and eqn 1[21] that relates the chemical shift difference, $\Delta\omega$, below the coalescence temperature, T_c, to the rate constant at coalescence, k_c, an approximation. This constant then was statistically corrected for the rotation of two equivalent rings by dividing it by 2 to give a value of 66/s. It then was further corrected for the unequal populations[22,23] of the *anti* and *syn* forms by multiplying 66/s by the mole fraction $(1/(1 + K))$ for the lower energy *anti* and $(K/(1 + K))$ for the higher energy *syn* isomer, where K is the ratio of *anti* to *syn* isomers, estimated to be about 3.2 from the observations at lower temperatures. Thus, k (*anti* to *syn*) is 16/s and k (*syn* to *anti*) is 50/s. Therefore, the free energy of activation at T_c for rotation from the *anti* ground state is 11 kcal/mol.

$$k_c = \pi\Delta\omega\sqrt{2} \qquad (1)$$

The 2′-Pz compound also gave sharp signals with integer area ratios consistent with the presence of a time-

(16) Bolm, C.; Ewald, M.; Felder, M.; Schlingloff, G. *Chem. Ber.* **1992**, *125*, 1169.
(17) Seyferth, D.; Vick, S. C. *J. Organomet. Chem.* **1977**, *141*, 173.
(18) Farina, V. *Pure Appl. Chem.* **1996**, *68*, 73.
(19) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
(20) Yamamoto, Y.; Yanagi, A. *Chem. Pharm. Bull.* **1982**, *30*, 1731.
(21) Binsch, G. *Top. Stereochem.* **1968**, *3*, 97.
(22) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; J. Wiley & Sons: New York, 1994.
(23) Shanan-Atidi, H.; Bar-Eli, K. H. *J. Phys. Chem.* **1970**, *74*, 961.

averaged spectrum at ambient temperatures in DMSO-d_6, $CDCl_3$, or THF-d_4. This compound in $CDCl_3$ at −35 °C demonstrated some slight broadening for the pyrazinyl protons. At −100 °C in a mixture of $CDCl_3$−acetone-d_6, evidence for the existence of the two diastereomers was ambiguous, as was the case with THF-d_4 solvent at −90 °C. Some new, small peaks did appear, but they were largely overlapped by major peaks.

The interpretation of the spectral changes for the 3′,4″ isomer is straightforward. In DMSO-d_6 at 20 °C, *two* sets of broadened signals for the diastereotopic protons of the 4″-pyridyl group were evident, but they were partially overlapped by the sharp signals for the 3′-pyridyl ring, consistent with slow rotation of both rings. Because of this overlap, it was not possible to determine accurately the coalescence temperature, but we estimate T_c to be about 45 °C, which gave using eq 1 a rate constant of 85/s after dividing by 2 to provide the value for rotation from one of the two equivalent sites for a hydrogen atom. The free energy of activation for rotation about the pyridyl−naphthalene bond is about 16 kcal/mol, a value much in keeping with those observed for the rotation of phenyl rings in 1,8-diarylnaphthalenes.[2] Rotation of either pyridyl ring can bring about coalescence, and the barriers for each ring are expected to be similar. Although a statistical correction might therefore be applied for two equivalent rings, this was not done. Such a correction would only change the calculated energy barrier by 0.4 kcal/mol.

For the 2′,3″ isomer with 14 different protons, spectral changes were complex as the temperature was decreased. In acetone-d_6 at 22 °C, nine distinct multiplets were apparent with areas in integer ratios suggesting rapid rotation to give a population-weighted averaged spectrum. But at 19 °C some signals were sharp, while others broadened slightly. Signals began to merge at −30 °C and then became resolved into a complex pattern of multiplets at −60 °C, which essentially did not change at −90 °C.

All the signals in the spectrum of the 2′,4″ isomer in DMSO-d_6 were sharp at 19 °C. If the diastereotopic protons are not accidentally degenerate, then rotation is rapid and the coalescence temperature must be below 19 °C. Low-temperature studies were not undertaken.

Semiemperical Computations. A slight preference in the computed equilibrium constant exists for the *anti* over the *syn* diastereomer in **1**−**3** and **6**.[11] This constant at 20 °C for the 2′,2′ or the 2′-Pz compounds (DMSO solvent) is 7.6 (AM1) or 3.9 (PM3), and for the 2′,3″ it is 1.6 (AM1) or 1.3 (PM3). We find at −55 °C the *anti*/*syn* ratio for the 2′,2′ isomer to be 3.2. *Anti-syn* conformations are not possible for isomers **4** and **5** with a 4″-pyridyl ring.

Table 1 lists the activation enthalpies for rotation about the σ-bond to two of the limiting transition states in DMSO solvent, TS1 where a CH bond of one ring is directed at the face of the other ring and TS2 where an annular nitrogen atom is directed at the other face. The lower energy *anti* conformation is the reference structure for **1**−**3** and for **6** reported earlier.[11] Values also are given for the rotation of each ring when the two pyridyl rings are different as in **3**−**5**.

There are two clusters of numerical values in Table 1. When the ring nitrogen atom at a 2′ position on the pyridyl or pyrazinyl ring is directed at the other hetaryl ring in TS2, the average energy for the four relevant compounds **1**−**4** is 9.1 (AM1) or 9.3 (PM3) kcal/mol. But in TS2 when a ring nitrogen atom located at a 3′ position is directed at the other ring as in **3**, **5**, and **6**, the average energy for these three increases to 13.5 (AM1) or 13.2 (PM3) kcal/mol. The average for all six substrates in TS1 is 14.2 (AM1) or 12.9 (PM3) kcal/mol. The small differences in the two sets of larger values may not be meaningful, but the difference of about 4 kcal/mol between the large and small sets of values has considerable significance.

Table 1. Activation Enthalpies (kcal/mol) for Rotation to Either Transition State 1 (TS1) where a CH Bond Is Directed at the Second Ring or to Transition State 2 (TS2) where a Nitrogen Atom Is Directed at the Second Ring[a]

compd	TS1, AM1	TS1, PM3	TS2, AM1	TS2, PM3	rotated ring
1, (2′,2′)[b]	15.9	13.2	9.5	9.7	2′-Py
2, (2′-Pz)[b]	16.3	13.2	8.2	8.5	2′-Pz
3, (2′,3″)[b]	14.9	12.5	9.4	9.6	2′-Py
3, (2′,3″)[b]	13.8	13.4	14.5	13.7	3′-Py
4, (2′,4″)	15.0	12.5	9.3	9.4	2′-Py
4, (2′,4″)	14.1	13.6			4′-Py
5, (3′,4″)	12.5	12.5	13.0	12.8	3′-Py
5, (3′,4″)	12.6	12.7			4′-Py
6, (3′,3′)[b]	12.4	12.6	13.1	13.0	3′-Py

[a] Computed for DMSO solvent. [b] *Anti* conformation taken as the reference.

Discussion

The computations show the naphthalene ring to be slightly twisted out of planarity in the ground state[24] and considerably more deformed in the two rotational transition states. The *peri* carbon atoms at the 1 and 8 positions are located above and below the main ring plane, thereby minimizing eclipsing of the σ-bonded rings. Thus, in the ground state the dihedral angle of twist defined by the σ-bonds from the two *peri* carbon atoms to the pyridyl rings is about 20° and in a typical rotational transition state the value is about 55°. The hetaryl rings in the ground state are shifted off center and are stacked. Such ground-state deformations also appear in various crystal structures.[25−27]

A "T-shaped" geometry for a rotational transition state has two primary sites of interaction: the edge and face of the two hetaryl rings and the edge of one of these rings and the edge of the naphthalene.

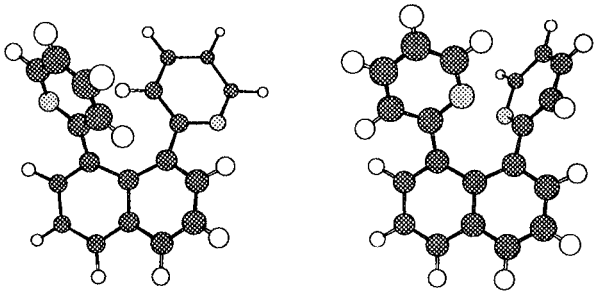
The computations show that a T-shaped geometry represents an idealized orientation. Both hetaryl rings are twisted with respect to the naphthalene plane, and the edge-to-face geometry does not place the two hetaryl rings in a perpendicular orientation. Rather, these two rings are tilted with respect to each other. Importantly, in order to minimize repulsive interactions, the rotating rings are splayed apart from the site of bonding to the naphthalene ring. Consequently, only *one* of the two ring protons at the edge, that hetaryl proton located *ortho* to the site of attachment, is directed toward the second face in a transition state (TS1). When an equivalent position is occupied by an annular nitrogen atom as in a 2′-pyridyl or 2′-pyrazinyl ring, then only the nitrogen atom along

(24) Kranz, M.; Clark, T.; Schleyer, P. v. R. *J. Org. Chem.* **1993**, *58*, 3317.
(25) Ljungstrom, E.; Lindquist, O.; Overbeck, O. *Acta Crystallogr., Sect. B* **1978**, *34*, 1727.
(26) House, H. O.; Koepsell, D. G.; Campbell, W. J. *J. Org. Chem.* **1972**, *37*, 1003.
(27) Jones, P. G.; Grahn, W.; Bahl, A.; Chrapkowski, A. *Z. Kristallogr.* **1995**, *210*, 229.

the edge points toward the opposite face (TS2). More removed nitrogen atoms such as those in the 3′- and 4′-pyridyl rings do not significantly interact with the second ring in the transition state.

At the site of interaction involving the naphthalene ring in the transition state for rotation, eclipsing of the hetaryl ring with the *ortho* site of naphthalene is only partial. Because the naphthalene ring is twisted out of planarity and the rotating hetaryl ring is skewed with respect to this ring, there is only partial eclipsing of the two rings. The data in Table 1 show that the energies are essentially the same whether or not a nitrogen atom or a CH group is directed at this position.

The two computed transition-state structures for the 2,2′ isomer are given in perspective drawings (TS(CH points in) and TS(N points in)). They show that only one site is significantly involved with the face of the second hetaryl ring.



TS (CH points in) **TS (N points in)**

There is a preference of some 4 kcal/mol for that conformation that places an *ortho* annular nitrogen atom in the face of the opposite ring in a rotational transition state (TS2). Therefore, those substrates with two different pyridyl rings, one of which is a 2′-pyridyl group, will show a preference for rotation of the 2′-pyridyl ring, i.e., the 2′-pyridyl ring will rotate faster than its 3′ or 4′ substituted isomeric rings. Thus, by this measure, an *ortho* nitrogen atom is smaller than a CH group.

A number of measures indicate that the "size" of an electron pair on a nitrogen atom is smaller than that of a proton, including, for example, conformational studies such as those comparing cyclohexanes and piperidines,[28] rotational energy barriers in biphenyls and bipyridines,[29] and investigations dealing with lifetimes of optically active compounds. For example, the rate of racemization at low temperature of 1-(1′-naphthyl)isoquinoline is slightly faster than that of 1,1′-binaphthyl.[30,31]

Computational and experimental studies suggest that pyridine and pyrazine dimers in the gas phase may occupy a geometry in which the two rings bond together through a nitrogen atom.[32,33] Perhaps such attractive interactions also exist in our rotational transition states.

Conclusions. The rotational energy barriers associated with the hetaryl rings in **1**−**6** are much smaller when there is a nitrogen atom located at an *ortho* site as in a 2′-pyridyl or 2′-pyrazinyl ring than when a nitrogen atom is situated *meta* or *para* as in a 3′- or 4′-pyridyl ring. The free energy of activation for rotation from the *anti* ground state of the 2′-pyridyl ring in **1** is 11 kcal/mol (−55 °C) and for the 3′- or 4′-pyridyl ring in **5** it is 16 kcal/mol (45 °C). To the extent that the free energies are temperature independent,[7] they are similar to the computed enthalpy values in Table 1, 9.1 (AM1) or 9.3 kcal/mol (PM3) and 13.5 (AM1) or 13.2 kcal/mol (PM3), respectively.

Experimental Section

All of the proton NMR spectra were obtained at 300 MHz at 19−20 °C unless indicated otherwise. All coupling constants (*J*) are in Hz.

1,8-Di(2′-pyridyl)naphthalene (1) from 1,8-Dibromonaphthalene (7). A solution of 7.46 g (20.2 mmol) of 2-(tributylstannyl)pyridine,[16] 1.93 g (6.77 mmol) of **7**,[10] and 1.00 g (0.87 mmol, 6 mol %) of $Pd(Ph_3P)_4$ in 50 mL of degassed toluene was refluxed under dry nitrogen for 48 h. The cooled, filtered solution was concentrated in vacuo, and the dark brown oil was dissolved in 50 mL of dichloromethane and extracted with 70 mL of 2 N HCl. The aqueous layer was extracted again with dichloromethane (2 × 30 mL). The aqueous phase was adjusted to pH 14 with solid NaOH; the liberated base was extracted with dichloromethane (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), the solvent was removed, and the resultant brown oil was chromatographed on alumina using EtOAc in hexanes (10−50%). Drying in vacuo at 100 °C gave 790 mg (2.80 mmol, 41%) of an off-white solid. An analytical sample, mp 151−153 °C, was recrystallized from EtOAc: ^{1}H NMR ($CDCl_3$) δ 8.34 (dq, 2H, J = 1.2, 2.1, 5.1), 8.02 (dd, 2H, J = 1.5, 8.4), 7.71 (dd, 2H, J = 1.2, 6.9), 7.62 (t, 2H, J = 7.5), 7.20 (td, 2H, J = 1.8, 7.8), 6.97 (dt, 2H, J = 1.2, 7.8), 6.82 (ddd, 2H, J = 1.2, 5.1, 7.5). Anal. Calcd for $C_{20}H_{14}N_2$: C, 85.08; H, 5.00; N, 9.92. Found: C, 85.23; H, 4.96; N, 9.95.

1,8-Di(2′-dipyridyl)naphthalene (1) from 1,8-Bis(trimethylstannyl)naphthalene (8). A mixture of 340 mg (0.75 mmol) of **8**[17] 100 mg (0.087 mmol) of $Pd(Ph_3P)_4$, and 450 mg (2.41 mmol) of 2-bromopyridine in 10 mL of degassed anhydrous THF and 5 mL of *N*,*N*′-dimethylformamide (DMF) was heated at reflux for 3 d. After concentration, the brown oil was chromatographed on alumina using EtOAc in hexanes (20−100%) to yield 60 mg (0.21 mmol, 28%) of a white solid having the same NMR as that above.

1,8-Di(2′-pyrazinyl)naphthalene (2). A mixture of 420 mg (0.926 mmol) of **8**,[17] 110 mg (0.095 mmol) of $Pd(Ph_3P)_4$, 430 mg (3.75 mmol) of 2-chloropyrazine, and 5 mL of nitrogen-degassed anhydrous DMF was heated to 100−130 °C under nitrogen for 3 d. After removal of the solvent, the dark solid residue was dissolved in chloroform and chromatographed on alumina, eluting with EtOAc in hexanes (20−100%), and rechromatographed on silica (EtOAc) to remove traces of catalyst to yield 85 mg (0.30 mmol, 32%) of an off-white solid: mp 178−180 °C. ^{1}H NMR ($CDCl_3$) δ 8.61 (d, 2H, J = 1.8), 8.15 (d, 2H, J = 2.4), 8.10 (dd, 2H, J = 2.4, 7.2), 8.08 (m, 2H), 7.66 (m, 4H). Anal. Calcd for $C_{18}H_{12}N_4$: C, 76.04, H, 4.25, N, 19.71. Found: C, 76.42; H, 4.26; N, 19.86.

1-(2′-Pyridyl)-8-(3″-pyridyl)naphthalene (3) from 1-Bromo-8-(2′-pyridyl)naphthalene (10). A mixture of 270 mg (0.95 mmol) of **10**, 280 mg of diethyl(3-pyridyl)borane, 110 mg (0.095 mmol) of $Pd(PPh_3)_4$, 10 mL of degassed THF, and 450 mg of K_2CO_3 in 10 mL of H_2O was refluxed for 14 h. The cooled layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic phase was washed with brine (40 mL) and dried ($MgSO_4$). The oily residue from the concentrate was chromatographed on neutral alumina using EtOAc to yield 172 mg (0.61 mmol, 64%) of a white solid): mp 146−148 °C; ^{1}H NMR (acetone-d_6 at 22 °C) δ 8.32 (d, 1H, J = 1.2), 8.23 (d, 1H, J = 4), 8.13 (m, 3H), 7.65 (m, 3H), 7.45 (d, 1H, J = 6.9), 7.37 (t, 1H, J = 6.9), 7.24 (d, 1H, J = 8.1), 7.07 (d, 1H, J = 6.9), 6.89 (m, 2H). Anal. Calcd for $C_{20}H_{14}N_2$: C, 85.05, H, 5.00; N, 9.92. Found: C, 84.88; H, 5.09; N, 9.84.

1-(2′-Pyridyl)-8-(3″-pyridyl)naphthalene (3) from 1-Bromo-8-(3′-pyridyl)naphthalene[13] (9). A mixture of 300 mg

(28) Crabb, T. A.; Katritzky, A. R. *Adv. Heterocycl. Chem.* **1984**, *36*, 1.
(29) Fabian, W. M. F. *J. Comput. Chem.* **1988**, *9*, 369.
(30) Pedersen, J. R. *Acta Chem. Scand.* **1972**, *26*, 929.
(31) Pedersen, J. R. *Acta Chem. Scand. A* **1974**, *28*, 213.
(32) Sagarik, K.; Spohr, E. *Chem. Phys.* **1995**, *199*, 73.
(33) Wanna, J.; Bernstein, E. R. *J. Chem. Phys.* **1986**, *85*, 3243.

(1.06 mmol) of **9**, 1.50 g (4.08 mmol) of 2-(tributylstannyl)-pyridine,[16] and 60 mg (0.052) of $Pd(Ph_3)_4$ in 10 mL of toluene was heated under nitrogen at reflux for 24 h. After the toluene was removed under reduced pressure, 10 mL of DMF was added, and the solution was heated to dissolve the precipitate; the brown solution turned black, but the heating was continued for 24 h. The solvent was removed in vacuo; the residue was dissolved in 30 mL of $CHCl_3$ and extracted with 50 mL of 2 N HCl. The acid layer was washed with $CHCl_3$ (2 × 30 mL) and then adjusted to pH 14 with solid NaOH. After extraction with $CHCl_3$ (3 × 30 mL), drying ($MgSO_4$), and solvent evaporation, the residue was purified on neutral alumina using methanol in ethyl acetate (0−50%) to yield 83 mg (0.29 mmol, 27%) of a colorless solid. The analytical sample was recrystallized from ethyl acetate, mp 146−148 °C.

1-(2′-Pyridyl)-8-(4″-pyridyl)naphthalene (4). A mixture of 340 mg (1.20 mmol) of **10**, 500 mg (1.36 mmol) of 4-(tributylstannyl)pyridine,[16] and 115 mg (0.1 mmol) of $Pd(Ph_3P)_4$ in 5 mL of dry DMF was heated under nitrogen for 4 h at 140 °C. The solvent was evaporated under reduced pressure, the residue was dissolved in 30 mL of CH_2Cl_2, and the mixture was filtered. The filtrate was extracted with 2 N HCl (50 mL); the aqueous phase was washed with CH_2Cl_2 (2 × 30 mL) and then adjusted to pH 14 with solid NaOH. Following extraction with CH_2Cl_2, the combined organic phase was dried ($MgSO_4$) and solvent evaporated. Purification by chromatography on silica using methanol in EtOAc (10 → 20%) yielded 274 mg (0.972 mmol, 80%) of a white solid: mp 184−186 °C; ^{1}H NMR (DMSO-d_6 at 60 °C) δ 8.18 (d, 1H, J = 4), 8.13 (m, 4H), 7.68 (t, 1H, J = 7.2), 7.66 (t, 1H, J = 7.2), 7.58 (dd, 1H, J = 1.2, 7.2), 7.44 (dd, 1H, J = 1.5, 7.2), 7.38 (td, 1H, J = 1.8, 7.8), 7.10 (dd, 1H, J = 1, 8.7), 6.92 (m, 3H). Anal. Calcd for $C_{20}H_{14}N_2$: C, 85.05; H, 5.00; N, 9.92. Found: C, 85.08; H, 4.96; N, 9.88.

1-(3′-Pyridyl)-8-(4″-pyridyl)naphthalene (5). A mixture of 340 mg (1.20 mmol) of **9**, 1.10 g of 4-(tributylstannyl)-pyridine,[20] and 115 mg (0.1 mmol) of $Pd(Ph_3P)_4$ in 10 mL of dry DMF under nitrogen was stirred at 140 °C for 48 h. Solvent was removed under reduced pressure to give a yellow oil that was dissolved in 30 mL of CH_2Cl_2 and extracted with 50 mL of 2 N HCl. The aqueous layer was washed with $CHCl_3$ (2 × 30 mL) and adjusted to pH 14 with solid NaOH. The CH_2Cl_2 extract (3 × 30 mL) was dried and concentrated in vacuo, and the yellow solid was purified by column chromatography on neutral alumina using methanol in EtOAc (0−10%). After drying at 100 °C in vacuo, the off-white solid (165 mg, 0.58 mmol, 48%) gave an analytical sample by recrystallization from ethanol−ethyl acetate; mp 198−200 °C. ^{1}H NMR (DMSO-d_6 at 90 °C) 8.21 (d, 1H, J = 1.8), 8.2 (m, 5H), 7.66 (t, 1H, J = 7.5), 7.64 (t, 1H, J = 7.5), 7.41 (t, 2H, J = 6.6) 7.31 (dt, 1H, J = 2.1, 7.5), 6.93 (m, 3H). Anal. Calcd for $C_{20}H_{14}N_2$: C, 85.05; H, 5.00; N, 9.92. Found: C, 84.98; H, 4.94; N, 9.89.

1-Bromo-8-(3′-pyridyl)naphthalene[13] (9). A mixture of 395 mg (1.38 mmol) of **7**,[10] 185 mg (1.26 mmol) of diethyl(3-pyridyl)borane, 75 mg (0.0649 mmol, 5.15 mol %) of $Pd(PPh_3)_4$, 500 mg of K_2CO_3 in 10 mL of degassed H_2O, and 10 mL of degassed THF was refluxed under nitrogen for 3.5 h. The cooled mixture was diluted with ether (50 mL), and the extract was dried ($MgSO_4$) and concentrated under reduced pressure to a yellow-green oil (640 mg) that was purified on a silica column using hexanes/ethyl acetate (1/1) to yield 270 mg (0.950 mmol, 75% based on borane) of a slightly yellow oil: ^{1}H NMR δ (DMSO-d_6) 8.61 (dd, 1H, J = 1.8, 4.8), 8.50 (dd, 1H, J = 0.9, 2.4), 8.13 (dd, 1H, J = 1.2, 8.2), 8.12 (dd, 1H, J = 1.2, 8.2), 7.87 (dd, 1H, J = 1.2, 7.2), 7.74 (dt, 1H, J = 1.5, 8.4), 7.66 (t, 1H, J = 7.8), 7.46 (m, 3H). Anal. Calcd for $C_{15}H_{10}BrN$: C, 63.40; H, 3.55; N, 4.93. Found: C, 63.51; H, 3.64; N, 5.22.

1-Bromo-8-(2′-pyridyl)naphthalene (10). A mixture of 1.00 g (3.50 mmol) of **7**,[10] 1.41 g (3.83 mmol) of 2-(tributylstannyl)pyridine,[16] and 200 mg (0.17 mmol) of $Pd(Ph_3P)_4$ in 10 mL of toluene was heated at reflux under nitrogen for 3 d. After the solvent was removed under reduced pressure, 30 mL of hexanes/ethyl acetate (4/1) was added, and the mixture was allowed to stand overnight to give a precipitate that was chromatographed on Kieselgel, eluting with EtOAc in hexanes (20−100%) to give 340 mg (1.20 mmol) of yellowish oil. The material was converted to its methiodide for analysis below: ^{1}H NMR (DMSO-d_6) δ 8.62 (d, 1H, J = 4), 8.11 (m, 2H), 7.85 (m, 2H), 7.63 (t, 1H, J = 8), 7.5 (m, 4H).

1-Bromo-8-(1′methylpyridin-1′-ium-2′-yl)naphthalene. To 650 mg (2.28 mmol) of **10** in 2 mL of MeOH was added 0.5 mL (8 mmol) of methyl iodide. After 14 h at rt, the solvent was removed under reduced pressure, and the residue was dissolved in 2 mL of hot ethanol, made cloudy by the addition of ether, and allowed to crystallize at 0 °C for 4 h. The crystals were washed with ether and dried in vacuo at 100 °C to give an off-white solid (780 mg, 1.83 mmol, 80%): mp 215−217 °C. ^{1}H NMR (DMSO-d_6) δ 9.21 (dd, 1H, J = 0.5, 6), 8.66 (td, 1H, J = 1.5, 8.1), 8.40 (dd, 1H, J = 2.7, 7.2), 8.26 (m, 3H), 8.02 (dd, 1H, J = 1.5, 7.5), 7.84 (m, 2H), 7.60 (t, 1H, J = 7.8). Anal. Calcd for $C_{16}H_{13}BrIN$: C, 45.10; H, 3.08; N, 3.29. Found: C, 45.12; H, 2.99; N, 3.19.

Semiempirical Computations. Only two limiting transitions states are possible for the 2′,2′-dipyridyl and dipyrazinyl compounds, three for the 2′,4″, and four for the 2′,3″-dipyridyl materials. More possibilities arise for the latter depending on which pyridyl ring is rotated with respect to the other and whether the nitrogen or hydrogen atom is directed to the opposite face in the T-shaped transition state. All such limiting conformations were examined.

All calculations were done by the semiempirical AM1[34] and PM3[35,36] methods using the VAMP program package. Geometries were completely optimized (keyword PRECISE) using the eigenvector following method.[37] Solvent effects (DMSO) were included by the self-consistent reaction field approximation.[38] Transition states for *anti*/*syn* interconversion were approximately located by the reaction coordinate method (using 15° increments for the naphthalene−(het)aryl dihedral angle as a reaction coordinate while completely optimizing all other structural parameters) and refined by gradient norm minimization (keyword NS01A in VAMP). Especially in sterically demanding structures, such an approach may cause problems, e.g., a dependence of the calculated rotational barrier on the starting structure or the direction of the reaction path.[39,40] Generally, rotations of the (het)aryl groups in either direction for both the *syn* as well as the *anti* form were calculated.

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(34) Dewar, M. J. S.; Zoebisch, E. G.; Healey, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
(35) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209.
(36) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 221.
(37) Baker, J. *J. Comput. Chem.* **1986**, *7*, 385.
(38) Rauhut, G.; Clark, T.; Steinke, T. *J. Am. Chem. Soc.* **1993**, *115*, 9174.
(39) Janoschek, R.; Fabian, W. M. F.; Kollenz, G.; Kappe, C. O. *J. Comput. Chem.* **1996**, *15*, 132.
(40) Boyd, D. B.; Smith, D. W.; Stewart, J. J. P.; Wimmer, E. *J. Comput. Chem.* **1988**, *9*, 387.