Investigation of the Stereodynamics of Axially Chiral 1,8-Bis(2,2′-diphenyl-4,4′-dipyridyl)naphthalene and Cryogenic Separation of Its *syn*/*anti*-Isomers

Christian Wolf* and Gilbert E. Tumambac

Department of Chemistry, Georgetown University, Washington, D.C. 20057

Received: October 23, 2002; In Final Form: December 10, 2002

The kinetics of the *syn/anti*-isomerization of 1,8-bis(2,2′-diphenyl-4,4′-dipyridyl)naphthalene, **1**, was investigated over a wide temperature range using variable-temperature NMR spectroscopy in conjunction with dynamic HPLC and computer simulation. Rate constants obtained utilizing both methods between −65.0 and 40.3 °C were found to be in excellent agreement and allowed for the determination of the Gibbs standard activation energy $\Delta G^{\circ\ddagger}$ for the diastereoisomerization of **1** as 70.4 kJ/mol. The rotational activation enthalpy $\Delta H^{\ddagger}$ and the rotational activation entropy $\Delta S^{\ddagger}$ were calculated from the Eyring plot as 57.5 kJ/mol and −43.4 J/K mol, respectively. Cryogenic chromatography using an achiral HPLC column at −70 °C allowed the first separation of a stereolabile perisubstituted diarylnaphthalene into its *syn*- and *anti*-diastereoisomers, which interconvert at room temperature.

Introduction

A profound understanding of the structure−activity relationship of pharmaceuticals has become an integral part of today's drug development. Since the coexistence of conformational or configurational isomers of chiral compounds can have a significant impact on their pharmacological profile, it is important to study the stereodynamics of promising drug candidates. The striking differences in the pharmacological and toxicological effects of the enantiomers of thalidomide, which undergoes rapid racemization under physiological conditions, are well-known. Similarly, the stereochemical integrity of compounds that exhibit rotamers due to hindered rotation about a single bond needs to be carefully investigated. The interconversion of axially chiral, stereolabile compounds that afford a mixture of heavily populated conformations, such as atropisomeric naphthalene derivatives, have received increasing attention.[1] In particular, 1,8-disubstituted naphthalenes exhibiting alkyl,[2] aryl,[3] and hetaryl[4] groups have been synthesized to study stacked aryl interactions and the stereodynamic properties of these compounds. The design of axially chiral 1,8-diarylnaphthalenes exhibiting conformational stability at ambient temperature has been an ongoing challenge to organic chemists. The development of stable, C_2-symmetric *anti*-1,8-dihetarylnaphthalenes would afford a new class of bidentate ligands with various applications in chiral Lewis acid or chiral Lewis base-catalyzed asymmetric reactions. All attempts to incorporate severe steric strain into the 1,8-disubstituted framework to prevent atropisomer isomerization of this class of compounds have not been successful to date. A profound understanding of the stereodynamics of the interconversion process including enthalpic and entropic factors seems essential for developing stable 1,8-diarylnaphthalene-derived atropisomers. However, the determination of the activation enthalpy $\Delta H^{\ddagger}$ and activation entropy $\Delta S^{\ddagger}$ for the isomerization of 1,8-disubstituted naphthalene-derived atropisomers based on kinetic measurements over an extensive temperature range is still elusive.

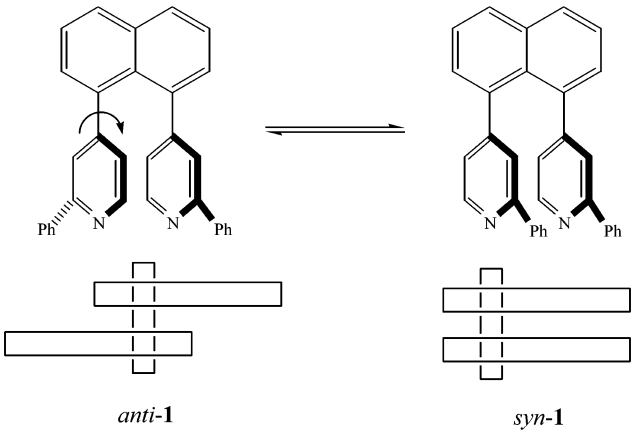

Figure 1. Isomerization of the two conformational diastereoisomers of 1,8-bis(2,2′-diphenyl-4,4′-dipyridyl)naphthalene, **1**, exhibing either parallel (*syn*) or antiparallel (*anti*) 2-phenylpyridyl rings.

Results and Discussion

We have recently developed a synthetic route toward 1,8-bis(2,2′-disubstituted-4,4′-dipyridyl)naphthalenes and their corresponding *N*,*N*′-dioxides and investigated the conformational stability of these atropisomers using variable-temperature NMR spectroscopy.[5] Herein, we report the investigation of the isomerization of 1,8-bis(2,2′-diphenyl-4,4′-dipyridyl)naphthalene, **1**, over a temperature range of more than 100 °C using dynamic HPLC and computer simulation (DHPLC) in conjunction with dynamic NMR spectroscopy (DNMR). The first separation of the *syn*- and *anti*-isomers of this class of compounds under cryogenic conditions is also reported, Figure 1.

Rotation of either pyridyl moiety of 1,8-bis(2,2′-diphenyl-4,4′-dipyridyl)naphthalene, **1**, results in isomerization between

* To whom correspondence should be addressed. E-mail: cw27@georgetown.edu.

10.1021/jp0272926 CCC: $25.00
Published on Web 01/15/2003

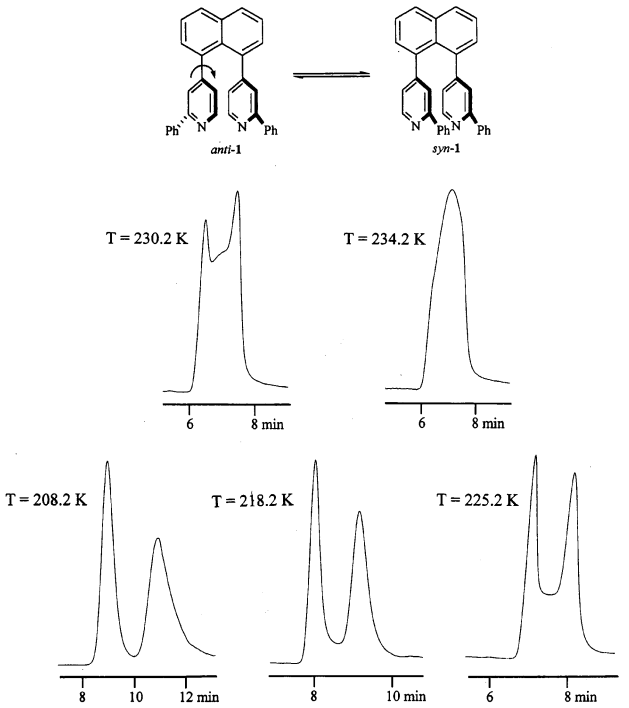

Figure 2. Cryogenic HPLC separations of the *syn*- and *anti*-isomers of **1** on a CN column at various temperatures.

the meso *syn*- and the axially chiral *anti*-isomers. NMR studies revealed an almost equimolar ratio of the diastereomers of **1** in solution.[5] The ratio did not change with time or after heating indicating a system at equilibrium. Apparently, the energies of the *syn*- and *anti*-diastereoisomers are not as different as one would intuitively expect since the pyridyl rings splay away from each other causing the phenyl groups not be in close contact, vide infra. The similar stability observed for the syn- and *anti*-isomers of **1** is in good agreement with *syn/anti*-ratios reported for similar 1,8-dihetarylnaphthalenes.[4b] The interconversion between the almost equienergetic rotamers of **1** was found to proceed fast at ambient temperature and the energy barrier to rotation about the chiral naphthylpyridyl axis was determined as 73 kJ/mol at 40.3 °C by DNMR. The separation of atropisomer **1** and structural analogues into enantiomers and diastereomers, respectively, proved to difficult.[6] Screening of a variety of achiral and chiral HPLC columns revealed that the separation of the diastereoisomers of **1** can be accomplished under cryogenic conditions. In addition, we observed temperature-dependent plateaus between the two separated peaks at elevated temperature, Figure 2.[7] These elution profiles are known to be a consequence of simultaneous interconversion and separation of isomers during the chromatographic run. Similar to variable-temperature NMR spectroscopy, computer simulation of the experimentally obtained HPLC elution profiles provides the rate constants of the observed stereomutation at the corresponding temperature.[8] As a consequence of fast isomerization of **1** relative to the HPLC time scale, peak coalescence was observed at −39.0 °C.

Computer simulation of the chromatograms obtained between −65.0 and −43 °C allowed us to determine the rate constants of the *syn/anti*-isomerization of **1**. The experimentally obtained and calculated elution profiles are in excellent agreement, Figure 3. The energy barrier to isomerization of **1** was determined as 67.8 kJ/mol at −65.0 °C. Comparison of our DHPLC and DNMR studies shows that the rotational energy barrier of **1** steadily enhances with increasing temperature to 73 kJ/mol at 40.3 °C due to an unfavorable entropy of activation. The results

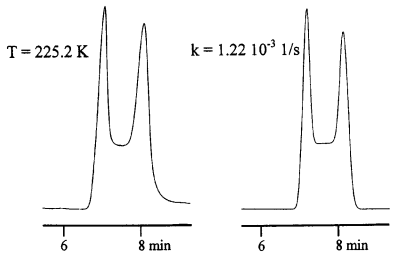

Figure 3. Experimentally obtained (left) and simulated elution profile (right). Computer simulations were obtained for a 1:1 diastereoisomer ratio using MimesisXP.

TABLE 1: Rotational Energy Barrier $\Delta G^{\ddagger}$ of 1 Determined by DHPLC and DNMR

entry	conditions[a]	temp (K)	$\Delta G^{\ddagger}$ (kJ/mol)	k (1/s)
1	hexanes/EtOH = 3:2	208.2	67.8[b]	$8.3\ 10^{-5}$
2	hexanes/EtOH = 3:2	218.2	68.3[b]	$4.0\ 10^{-4}$
3	hexanes/EtOH = 3:2	225.2	68.5[b]	$1.22\ 10^{-3}$
4	hexanes/EtOH = 3:2	230.2	68.7[b]	$2.5\ 10^{-3}$
5	$CDCl_3$	313.5	73.0[c]	9.03

[a] All chromatographic separations were achieved using a YMC CN column (column dimensions = 250 × 4.6 mm^2, flow rate = 1 mL/min, UV detection = 280 nm). [b]Determined by computer simulation of HPLC elution profiles. Average value of the isomerization in the mobile and stationary phase. [c] Determined by the coalescence method using variable-temperature NMR spectroscopy.[5b]

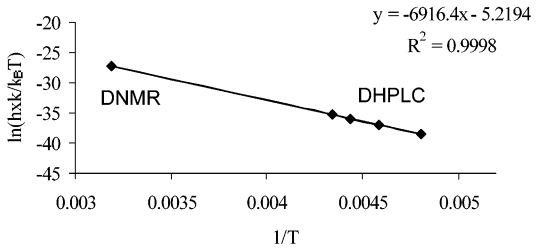

Figure 4. Eyring plot for the isomerization of **1**.

of the computer simulations are summarized in Table 1. Since the isomerization of **1** proceeds slowly under cryogenic conditions, we were able to achieve a baseline separation of the *syn*- and *anti*-isomers by HPLC at temperatures below −70 °C. The separation of rapidly interconverting 1,8-disubstituted naphthalenes into diastereoisomers in solution reported herein is unprecedented. It should be noted that some *syn*- and *anti*-isomers of 1,8-diarylnaphthalenes have been isolated in the solid state.[9]

Our results demonstrate that DHPLC and DNMR are complementary methods that allow kinetic investigations of stereolabile compounds over a wide temperature range, i.e., more than 100° C. Employing the Eyring eq 1, we were able to determine the activation enthalpy $\Delta H^{\ddagger}$ and activation entropy $\Delta S^{\ddagger}$ of the isomerization of atropisomer **1**. The Eyring plot demonstrates the excellent agreement of both methods, Figure 4. Since the experiments were conducted in chloroform and mixtures of hexanes and ethanol, respectively, one can conclude that solvent effects including hydrogen bonding on the rotational energy barrier of **1** are negligible. The activation enthalpy and entropy of the interconversion process were determined as 57.5 and −43.4 J/K mol, respectively. Accordingly, the Gibbs standard activation energy $\Delta G^{\circ\ddagger}$ for the *syn/anti*-isomerization of **1** was calculated as 70.4 kJ/mol.

$$k = k_B T/h[\exp(\Delta S^{\ddagger}/R)\exp(-\Delta H^{\ddagger}/RT)] \qquad (1)$$

The ground state conformations of the diastereoisomers of **1** were calculated by PM3 computations, Figure 5. Isomerization

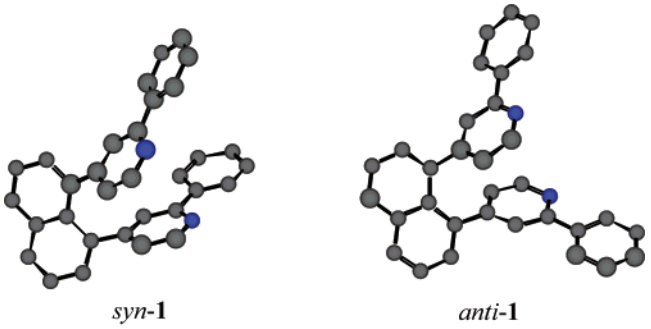

Figure 5. Ground state conformations of *syn*-**1** (left) and *anti*-**1** optimized by PM3 computations. Hydrogens are omitted for clarity.

requires one pyridyl ring to rotate about the chiral naphthyl-pyridyl axis. Thus, the edge of the rotating ring will be directed toward the adjacent pyridyl moiety in the transition state. In general, isomerization can proceed via two T-shaped transition states exhibing the phenyl ring of the rotating pyridyl moiety either pointed toward or away from the other pyridyl ring. The latter is expected to afford significantly less steric hindrance and should be favored. However, one would assume that in the transition state both pyridyl rings are significantly further splayed away from each other than in the ground states to minimize steric repulsion between the hydrogens in positions 5 and 6 of the rotating 2-phenylpyridyl ring and the pyridyl moiety in peri position. The small activation enthalpy and the considerably negative activation entropy calculated for **1** are indicative of a stereolabile atropisomer that interconverts through a highly ordered transition state. The design of conformationally stable 1,8-dihetarylnaphthalene-derived atropisomers requires the introduction of significantly enhanced steric hindrance to rotation. Incorporation of one substituent into the *ortho*-positions of 1,8-diarylnaphthalenes is known to impede isomerization but does not prevent interconversion at room temperature. Accordingly, Clough et al. determined the energy barrier to isomerization of 1,8-bis(2,2′-dimethyl-1,1′-diphenyl)naphthalene as 100 kJ/mol and reported slow isomerization between the two diastereoisomers at room temperature.[3f] On the bases of our results and precedent literature, one can expect that incorporation of substituents in positions 3 *and* 5 of each pyridyl moiety of **1** should sufficiently increase the rotational activation enthalpy to afford conformational stability. The preparation of such a framework is currently underway in our laboratories.

In summary, the stereodynamics including the Gibbs standard activation energy $\Delta G^{\circ\ddagger}$ the activation enthalpy $\Delta H^{\ddagger}$, and the activation entropy $\Delta S^{\ddagger}$ of the isomerization process of a 1,8-disubstituted naphthalene-derived atropisomers were investigated for the first time using DHPLC in conjunction with DNMR studies. It was thus demonstrated that DHPLC and DNMR afford two orthogonal methods that allow one to investigate the kinetics of stereolabile compounds, such as 1,8-bis(2,2′-diphenyl-4,4′-dipyridyl)naphthalene, **1**, over a wide temperature range. The Gibbs standard activation energy for the isomer interconversion of **1** $\Delta G^{\circ\ddagger}$ was determined as 70.4 kJ/mol. Accordingly, the separation of the diastereoisomers of **1** required cryogenic conditions and was accomplished by HPLC using a CN column at −70 °C. The low activation enthalpy and the considerably negative activation entropy of perisubstituted dipyridylnaphthalene **1** were attributed to an atropisomeric framework that is stereolabile at room temperature and undergoes isomerization through a highly ordered T-shaped transition state.

Acknowledgment. We thank Detlev Hochmuth (University of Hamburg, Germany) for helpful discussion and for the MimesisXP simulation software.

References and Notes

(1) Casarini, D.; Lunazzi, L.; Macciantelli, D. *Tetrahedron Lett.* **1984**, *25*, 3641−3642. (b) Casarini, D.; Lunazzi, L. *J. Org. Chem.* **1988**, *53*, 182−185. (c) Casarini, D.; Foresti, E.; Lunazzi, L.; Macciantelli, D. *J. Am. Chem. Soc.* **1988**, *110*, 4527−4532. (d) Casarini, D.; Davalli, S.; Lunazzi, L. *J. Org. Chem.* **1989**, *54*, 4616−4619. (e) Davalli, S.; Lunazzi, L. *J. Org. Chem.* **1991**, *56*, 1739−1747. (f) Villani, C.; Pirkle, W. H. *Tetrahedron: Asymm.* **1995**, *6*, 27−30. (g) Casarini, D.; Lunazzi, L. Mazzanti, A. *J. Org. Chem.* **1997**, *62*, 3315−3323. (h) Casarini, D.; Lunazzi, L. Mazzanti, A. *J. Org. Chem.* **1998**, *63*, 4746−4754. (i) Casarini, D.; Lunazzi, L. Mazzanti, A. *J. Org. Chem.* **1998**, *63*, 4991−4995. (j) Casarini, D.; Mazzanti, A.; Alvarez, A. M. *J. Org. Chem.* **2000**, *65*, 3200−3206. (k) Bragg, R. A.; Clayden, J.; Morris, G. A.; Pink, J. H. *Chem. Eur. J.* **2002**, *8*, 1279−1289. (l) Dell′Erba, C.; Gasparrini, F.; Grilli, S.; Lunazzi, L. Mazzanti, A.; Novi, M.; Pierini, M.; Tavani, C.; Villani, C. *J. Org. Chem.* **2002**, *67*, 1663−1668. (m) Wolf, C.; Pranatharthiharan, L.; Ramagosa, R. B. *Tetrahedron Lett.* **2002**, *43*, 8563−8567.

(2) (a) Fields, D. L.; Regan, T. H. *J. Org. Chem.* **1971**, *36*, 2986−2990. (b) Fields, D. L.; Regan, T. H. *J. Org. Chem.* **1971**, *36*, 2991−2995. (c) Fields, D. L.; Regan, T. H. *J. Org. Chem.* **1971**, *36*, 2995−3001.

(3) (a) House, H. O.; Magin, R. W.; Thompson, H. W. *J. Org. Chem.* **1963**, *28*, 2403−2406. (b) House, H. O.; Bashe, R. W. *J. Org. Chem.* **1965**, *30*, 2942−2947. (c) House, H. O.; Bashe, R. W. *J. Org. Chem.* **1967**, *32*, 784−791. (d) House, H. O.; Campbell, W. J.; Gall, M. *J. Org. Chem.* **1970**, *35*, 1815−1819. (e) House, H. O.; Koepsell, D. G.; Campbell, W. J. *J. Org. Chem.* **1972**, *37*, 1003−1011. (f) Clough, R. L.; Roberts, J. D. *J. Am. Chem. Soc.* **1976**, *98*, 1018−1020. (g) Cozzi, F.; Cinquini, M.; Annunziata, R.; Dwyer, T.; Siegel, J. S. *J. Am. Chem. Soc.* **1992**, *114*, 5729−5733. (h) Cozzi, F.; Cinquini, M.; Annunziata, R.; Siegel, J. S. *J. Am. Chem. Soc.* **1993**, *115*, 5330−5331 (i) Cozzi, F.; Ponzini, F.; Annunziata, R.; Cinquini, M.; Siegel, J. S. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1019−1020 (j) Pritchard, R. G.; Steele, M.; Watkinson, M.; Whiting, A. *Tetrahedron Lett.* **2000**, *41*, 6915−6918. (k) Cross, W.; Hawkes, G. E.; Kroemer, R. T.; Liedl, K. R.; Loerting, T.; Nasser, R.; Pritchard, R. G.; Steele, M.; Watkinson, M.; Whiting, A. *J. Chem. Soc., Perkin Trans. 2* **2001**, 459−467. (l) Steele, M.; Watkinson, M.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 588−598. (m) Thirsk, C.; Hawkes, G. E.; Kroemer, R. T.; Liedl, K. R.; Loertig, T.; Nasser, R.; Pritchard, R. G.; Steele, M.; Warren, J. E.; Whiting, A. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1510−1519.

(4) (a) Zoltewicz, J. A.; Maier, N. M.; Fabian, W. M. F. *Tetrahedron* **1996**, *52*, 8703−8706. (b) Zoltewicz, J. A.; Maier, N. M.; Fabian, W. M. F. *J. Org. Chem.* **1996**, *61*, 7018−7021. (c) Maier, N. M.; Zoltewicz, J. A. *Tetrahedron* **1997**, *53*, 465−468. (d) Zoltewicz, J. A.; Maier, N. M.; Fabian, W. M. F. *J. Org. Chem.* **1997**, *62*, 2763−2766. (e) Zoltewicz, J. A.; Maier, N. M.; Fabian, W. M. F. *J. Org. Chem.* **1997**, *62*, 3215−3219. (f) Zoltewicz, J. A.; Maier, N. M.; Lavieri, S.; Ghiviriga, I.; Abboud, K. A. *Tetrahedron* **1997**, *53*, 5379−5388.

(5) (a) Wolf, C.; Ghebremariam, B. T. *Synthesis* **2002**, 749−752. (b) Wolf, C.; Ghebremariam, B. T. *Tetrahedron: Asymm.* **2002**, *13*, 1153−1156.

(6) We were not able to separate the stereoisomers of 1,8-bis(2, 2′-dimethyl-4, 4′-dipyridyl)naphthalene, 1,8-bis(2, 2′-dimethyl-4, 4′-dipyridyl)-naphthalene-*N*,*N*′-dioxide, and 1,8-bis(2, 2′-diphenyl-4, 4′-dipyridyl)-naphthalene-*N*,*N*′-dioxide using a broad variety of achiral and chiral columns under cryogenic conditions.

(7) The isomers were separted on a commercially available YMC CN column (250 mm × 4.6 mm) using a Hewlett-Packard 1050 HPLC equipped with an HP diode array detector and Chemstation software. Samples were dissolved in the mobile phase (hexanes/EtOH = 3: 2) in a concentration of 1 mg/mL. The temperature was measured with a calibrated thermometer and held constant through the run. The column was allowed to equilibrate at the chosen temperature for 10 min prior to each sample injection.

(8) For a recent review on dynamic chromatography and computer simulation, see: Trapp, O.; Schoetz, G.; Schurig, V. *Chirality* **2001**, *13*, 403−414.

(9) (a) Beagley, B.; Edge, N. C.; Jaiboon, N,; James, J. J.; McAuliffe, C. A.; Thorp, M. S.; Watkinson, M.; Whiting, A.; Wright, D. C. *Tetrahedron*, **1996**, *52*, 10193−10204. (b) Cross, W.; Hawkes, G. E.; Kroemer, R. T.; Liedl, K. R.; Loerting, T.; Nasser, R.; Pritchard, R. G.; Steele, M.; Watkinson, M.; Whiting, A. *J. Chem. Soc., Perkin Trans. 2* **2001**, 459−467.