

Racemization Energy of 3,2'-Tetramethylene-2-phenyl-6-(pyrid-2''-yl)pyridine Estimated by Temperature Variation ¹H NMR Experiment

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Received October 27, 2012, Accepted November 11, 2012

Key Words : Racemization energy, 3,3'-Tetramethylene-2-phenyl-6-(pyrid-2''-yl)pyridine, Temperature variation H NMR, Conformational rigidity

Studies on the conformation of annulated bi-aryls have long been pursued extensively due to interest in the chirality and spectroscopic properties of conformationally restricted bi-aryls and their possible use in the determination of the absolute configuration of atropisomeric biaryls.¹ One of the most extensively studied systems is 2,2'-polymethylenebiphenyls (**1**), of which the chirality depends on the biphenyl unit as the stereogenic element.²

Gottlieb *et al.*⁴ suggests that 2,2'-tetramethylenebiphenyl (**1d**, 1,2,3,4-dibenzo-1,3-cyclooctadiene) can exist in solution in two conformations, a nonsymmetrical twist-boat (TB) and a twist-boat-chair (TBC) with C_2 symmetry, in nearly equal populations. These conformations interconvert *via* two processes: (A) **I** (**IV**) \rightleftharpoons **II** (**III**) and (B) **II** \rightleftharpoons **III** (Figure 1), of which process (A) has been suggested as a preferred one based on data from X-ray diffraction and ¹H and ¹³C NMR spectra. The difference between the TB and TBC conformations has been estimated by ¹H NMR spectroscopy to be 11.8 kcal/mol, the latter being lower in steric energy.⁵ However, the energy barrier between the two TB

conformations (**II** and **III**) of has been estimated to be 23.1 kcal/mol,⁶ which is high enough to prevent from inter-conversion of the two enantiomers.⁷ This energy barrier may lead the loss of flexibility on the bridge to be rigid, thus the two conformational enantiomers **I** and **IV** are not readily inter-convertible. The energy barrier between the two conformational enantiomers **I** and **IV** was, thus, estimated by thermal racemization to be 23.2 kcal/mol,⁸ which is reasonable agreement with 23.2 kcal/mol found by Dvorken *et al.*⁹ for the corresponding 10,11-dicarboxylic acid.

A plenty of annulated 2,2'-biheteroaryls¹⁰ have been reported in the literature and examined their conformational properties. The tetramethylene bridges of all systems are rigid at room temperature in the NMR time scale while trimethylene-bridges are flexible under the same condition except that of 3,3'-trimethylene-2-(quinolin-2'-yl)-4(3*H*)-quinazolinone. It should be noted that trimethylene-bridge of 3,3'-trimethylene-2-(quinolin-2'-yl)-4(3*H*)-quinazolinone is conformationally rigid at room temperature and thus the activation energy has been estimated by temperature vari-

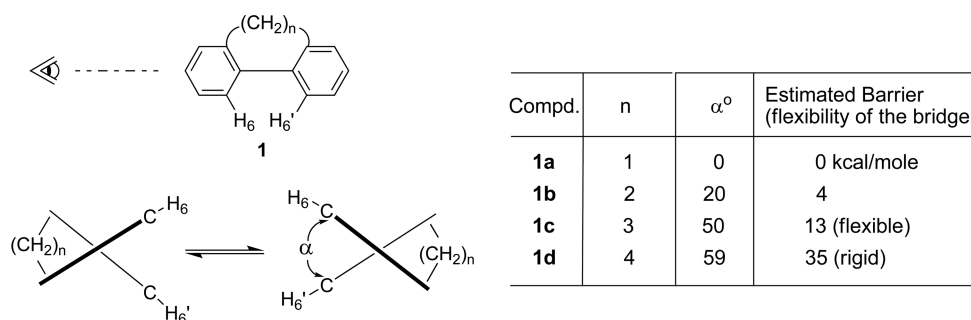


Figure 1. Relationship of length of the bridge and dihedral angle between the two phenyl ringplanes. Data were taken from Ref. 3.

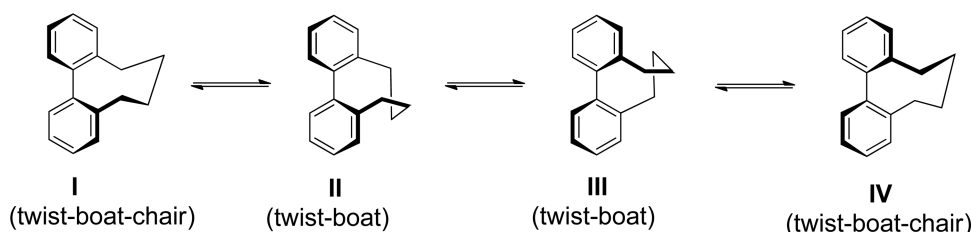


Figure 2. Possible conformational isomerism of 2,2-tetramethylenebiphenyl.

ation ^1H NMR method to afford the activation energies for inter-conversion of 15.7 kcal/mol.¹¹ However, all the attempts to resolve have not been successful as yet.

We herein reported the activation energy for the interconversion of conformational enantiomers of 3,2'-tetramethylene-2-phenyl-6-(pyrid-2''-yl)pyridine (**2**) estimated by ^1H NMR temperature variation experiment.

Results and Discussion

The required compound, 3,2'-tetramethylene-2-phenyl-6-(pyrid-2''-yl)pyridine (**2**), was prepared by employing previously reported method^{10d} and fully characterized by spectroscopic methods. All proton and carbon resonances were assigned based on the COSY, HMBC as well as HMQC. ^1H NMR temperature variation experiment was performed on a Bruker-250 spectrometer in $\text{DMSO-}d_6$.

The length of the bridging polymethylene unit is critical to induce the rigidity of the bridge. ^1H NMR spectrum has long been used as a probe to determine the flexibility of the annulating bridges. In annulated bi-aryls,^{10,11} ^1H NMR-spectra, specially the aliphatic regions, afforded information on the conformations of compounds which were highly dependent on the length of the bridge. The tetramethylene bridges on the systems examined are rigid at room temperature in the NMR time scale while the protons in di- and trimethylene-bridges in most of annulated biaryls are flexible enough to satisfy N+1 splitting rule.¹⁰ The aliphatic regions of ^1H NMR spectrum of **2** showed four different proton resonances indicating that all the eight protons were not magnetically equivalent (Figure 3).

Although ^{13}C NMR spectrum of **2** showed all required

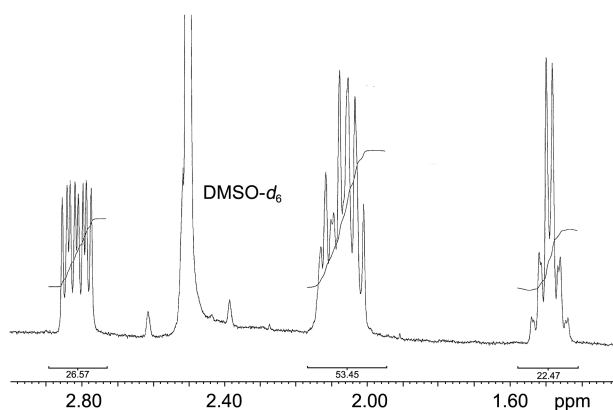


Figure 3. ^1H NMR spectrum of **2** (600 MHz, CDCl_3 , aliphatic region only).

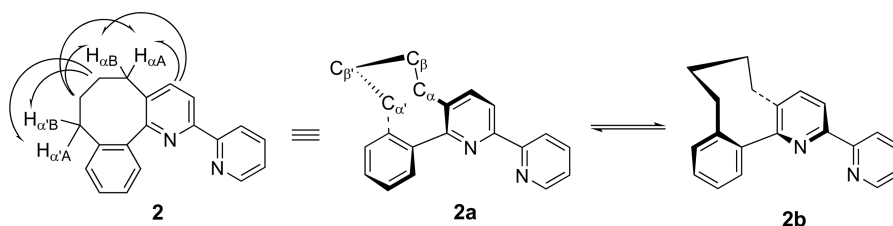


Figure 4. Enantiomers of **2** and selected ^1H - ^{13}C long-range correlations in HMBC spectrum.

numbers of 4 sp^3 -hybridized carbon resonances such as δ 32.56 ($\text{C}_{\alpha'}$), 31.80 (C_{α}), 29.29 ($\text{C}_{\beta'}$), and 29.00 (C_{β}), two protons of the each methylene unit adjacent to aromatic rings are experiencing magnetic non-equivalency more evidently, thus showing two doublets of doublets, respectively.^{10c-f} A hydrogen $\text{H}_{\alpha\text{A}}$ of the two H's on the carbon C_{α} adjacent to C3 of the central pyridine ring and that ($\text{H}_{\alpha'\text{A}}$) on the carbon ($\text{C}_{\alpha'}$) adjacent to C2 of phenyl ring lie the deshielding plane of the adjacent aromatic ring, respectively, thus are deshielded to δ 2.832 ($^2J = 13.5$, $^3J = 8.1$ Hz) and δ 2.790 ($^2J = 13.5$, $^3J = 8.1$ Hz). The other hydrogen $\text{H}_{\alpha\text{B}}$ on C_{α} and that ($\text{H}_{\alpha'\text{B}}$) on $\text{C}_{\alpha'}$ experience shielding effect of the adjacent phenyl and central pyridine, respectively, to give resonances overlapped in the region of δ 2.29-2.01.

Such correlation was confirmed by HMBC spectrum of **2**, in which ^1H - ^{13}C long-range correlations between C_{β} (δ 29.29) and two hydrogens $\text{H}_{\alpha'\text{A}}$ (δ 2.790) and $\text{H}_{\alpha'\text{B}}$ (δ 2.13-2.08), and similarly $\text{C}_{\beta'}$ (δ 29.00) to $\text{H}_{\alpha\text{A}}$ (δ 2.810) and $\text{H}_{\alpha\text{B}}$ (δ 2.29-2.01), respectively, were observed as shown in Figure 3. HMQC spectrum of **2** additionally confirmed ^1H - ^{13}C correlations between C_{α} (δ 31.80) and two hydrogens $\text{H}_{\alpha\text{A}}$ and $\text{H}_{\alpha\text{B}}$, and similarly $\text{C}_{\alpha'}$ (δ 32.56) to $\text{H}_{\alpha'\text{A}}$ and $\text{H}_{\alpha'\text{B}}$, respectively and similar correlation was observed between C_{β} and two hydrogens $\text{H}_{\beta\text{A}}$ and $\text{H}_{\beta\text{B}}$, and similarly $\text{C}_{\beta'}$ to $\text{H}_{\beta'\text{A}}$ and $\text{H}_{\beta'\text{B}}$.

In addition, vicinal coupling constants ($^3J = 8.1$ Hz) of $\text{H}_{\alpha\text{A}}$ would lead corresponding dihedral angles $\text{H}_{\alpha\text{A}}\text{-C}_{\alpha}\text{-C}_{\beta}\text{-H}_{\beta\text{A}}$ and $\text{H}_{\alpha\text{A}}\text{-C}_{\alpha}\text{-C}_{\beta}\text{-H}_{\beta\text{B}}$ 165.9° and 11.6°, respectively, from Karplus relationship.¹² These values were well matched to the values from X-ray crystal structure of **2**.¹³

Temperature variation experiment of the aliphatic region of 3,2'-tetramethylene-2-phenyl-6-(pyrid-2''-yl)pyridine led coalescence of two sets of resonances at 110 °C (Figure 5). The proton resonance at δ 2.830 for $\text{H}_{\alpha\text{A}}$ and a resonance at the region δ 2.13-2.01 as well as resonances δ 2.790 and δ 2.13-2.01 collapsed to two broad singlets at δ 2.790 and 2.110 at 110 °C. Such a time-dependent corresponding to coalescence could be explained that the rate of interconversion of the two conformational isomers would become comparable with the frequency difference between $\text{H}_{\alpha\text{A}}$ and $\text{H}_{\alpha\text{B}}$ as well as $\text{H}_{\alpha'\text{A}}$ and $\text{H}_{\alpha'\text{B}}$.¹⁴ Two geminal hydrogens at each carbon are equivalent to confirm flexibility of the bridge of **2** at 110 °C. The activation energy of the interconversion was, thus, calculated by previously employed equation¹⁵ to give 23 kcal/mol which was somewhat comparable to that of the corresponding carbon analogue (**1d**).

In conclusion, the racemization energy for the two conformational enantiomers of 3,2'-tetramethylene-2-phenyl-6-(pyrid-

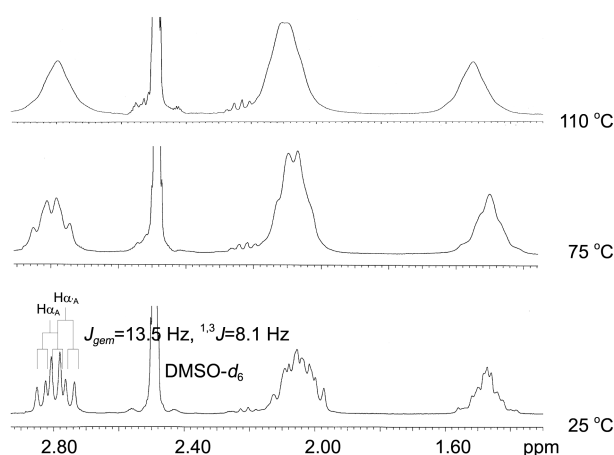


Figure 5. Temperature variation experiment of **2** (aliphatic region only).

2''-yl)pyridine was estimated by temperature variation ^1H NMR method to give 23 kcal/mole.

Experimental

3,2'-Tetramethylene-2-phenyl-6-(pyrid-2''-yl)pyridine (2). ^1H NMR (CDCl_3 , 600 MHz) δ 8.68 (d, 1H, $J = 4.8$ Hz, $\text{H6}''$), 8.36 (d, 2H, $J = 8.1$ Hz, $\text{H3}''$ and $\text{H5}''$), 7.88 (t, 1H, $J = 8.1$ Hz, $\text{H4}''$), 7.80 (d, 1H, $J = 8.1$ Hz, H4), 7.46-7.42 (m, 3H, $\text{H4}'$, $\text{H5}'$, $\text{H6}'$), 7.36-7.33 (m, 2H, $\text{H3}'$, $\text{H5}''$), 2.832 (dd, 1H, $J_{\text{gem}} = 13.5$ Hz, $J_{\text{vic}} = 8.1$ Hz, $\text{H}_{\alpha\text{A}}$), and 2.790 (dd, 1H, $J_{\text{gem}} = 13.5$ Hz, $J_{\text{vic}} = 8.1$ Hz, $\text{H}_{\alpha\text{A}}$), 2.29-2.01 (m, 4H), 1.52-1.44 (m, 2H). All the carbon resonances were assigned as follows: ^{13}C NMR (CDCl_3 , 62.5 MHz) δ 157.02 (C_6), 155.58 (C_2''), 152.88 (C_2), 149.44 (C_6''), 141.83 (C_2'), 139.25 (C_1'), 138.76 (C_4), 138.04 (C_5), 137.42 (C_4''), 129.51 (C_3'), 129.25 (C_6'), 129.02 (C_4'), 126.04 (C_5'), 124.16 (C_5''), 120.64 (C_3''), 119.84 (C_3), 32.56 (C_α), 31.80 (C_α'), 29.29 (C_β), 29.00 (C_β').

Acknowledgments. Financial support from National Re-

search Foundation (2010-0012473) is gratefully acknowledged.

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