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Relayed Proton Brake in *N*-Pyridyl-2-*iso*-propylaniline

Derivative: Two Brakes with One Proton

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ABSTRACT: The addition of methane sulfonic acid to *N*-(2,6-dimethylpyridin-4-yl)-*N*-methyl-2-*iso*-propylaniline led to the selective protonation of the pyridine nitrogen atom, resulting in a significant deceleration of the rotation rates around both N-pyridyl and N-(*i*-Pr)phenyl bonds through a relayed brake mechanism.

Molecular rotors, which can control the rate and direction of bond rotation by external stimuli, have received much attention in the field of molecular device.¹ Molecular brakes are one of the most fascinating classes of the molecular rotors, and the deceleration of a bond rotation has been achieved by a various external stimuli such as metal cations, acids, bases, halide anions, light and heat.² On the other hand, as far as we know, molecular brake involving the rotational deceleration of plural bonds upon a single protonation has so far not been reported.

Recently we found that in N-C axially chiral 2-*tert*-butyl-6-methylanilines **I** bearing various *para*-substituted phenyl groups on nitrogen atom, the rotational barriers around a chiral axis increase with electron-withdrawing ability of *para*-substituents X (Figure 1).³ Furthermore, on the basis of these results, a new type of molecular brake (remote proton brake) was developed.^{3,4} That is, the addition of methane sulfonic acid to *N*-(4-aminophenyl)-2-*iso*-propylaniline **II** selectively protonated the primary amino group (the conversion of the electron-donating amino group into the electron-attracting ammonium group) to bring about a considerable increase in the rotational barrier around N-(*i*-Pr)Ph bond (4 kcal/mol). This brake thus resulted from a remote structural change at the Ar [(4-NH₂)Ph] group but not at the rotating Ar [N-(*i*-Pr)Ph] group.

Figure 1. Correlation between the rotational barriers and the electronic effects in N-C axially chiral anilines, and the application to proton brakes.

In this paper, we report the effect of protonation on the stereodynamics of *N*-methyl-2-*iso*-propylanilines bearing a 2- or 4-pyridyl group on the nitrogen atom. It was revealed that aniline having a 4-pyridyl group leads to the more considerable brake than 2-pyridyl derivative upon protonation. Furthermore, in 4-pyridyl derivative, a double brake phenomenon, where the rotations around two N-Ar bonds are synchronously decelerated under a single protonation (relayed proton brake), was found.

In line with our previous findings in aniline derivatives **I** and **II**, we envisioned that *N*-pyridyl-2-*iso*-propylaniline derivatives would also lead to proton brake around N-(*i*-Pr)Ph bond through the selective protonation of the remote basic pyridine nitrogen. In addition, the strong electron-withdrawing character of the pyridyl group was expected to produce measurable rotational barriers around both the N-pyridyl and N-(*i*-Pr)Ph bonds allowing the experimental determination of barriers about two N-Ar bonds in the neutral and protonated states. Although the synthesis of *N*-(4-pyridyl)-2-*iso*-propylaniline was initially attempted, the coupling reaction of 2-*iso*-propylaniline with 4-halopyridine did not efficiently proceed.⁵ On the other hand, Buchwald-Hartwig amination of *iso*-propylaniline with 2-bromopyridine or 4-bromo-2,6-dimethylpyridine proceeded smoothly,⁶ and subsequent *N*-methylation gave the desired *N*-methyl-*N*-pyridyl-2-*iso*-propylanilines **1** and **2** in good yields (Scheme 1).

Scheme 1. Synthesis of *N*-methyl-*N*-pyridyl-2-*iso*-propylaniline derivatives **1** and **2**.

At room temperature, the ¹H-NMR peak corresponding to the two Me hydrogens of *iso*-propyl group in 2-pyridyl aniline **1** was broadened (Figure 2). When MeSO₃H (1.0 equiv) was added to **1** in toluene-*d*₈, the broad signal was splitted into two doublet signals. The non-

equivalency of two Me signals revealed an axial chirality owing to the rotational restriction around N-(*i*-Pr)Ph bond at the time scale of NMR in **1-H⁺**.

Figure 2. Signals of two Me groups in ¹H-NMR of **1** and **1-H⁺** at rt.

Variable temperature NMR (VT-NMR) experiments of **1** and **1-H⁺** were further conducted for the evaluation of the rotational barriers (Figure 3). In aniline **1**, the broad Me signal of *i*-Pr at 295 K was changed into a sharp doublet signal indicating quick N-(*i*-Pr)Ph bond rotation around 330 K, while it splitted into two doublet signals revealing an axial chirality around 280 K. In pyridinium derivative **1-H⁺**, non-equivalent two Me signals at 295 K were coalesced around 350 K. On the basis of the VT-NMR charts and the line shape simulation with WinDNMR,⁷ the rotational barriers around N-(*i*-Pr)Ph bond in **1** and **1-H⁺** were evaluated to be 15.1 and 17.2 kcal/mol, respectively. Although the rotational barriers of **1** and **1-H⁺** bearing electron-withdrawing 2-pyridyl and 2-pyridinium groups were much higher than those of 4-aminophenyl derivatives **II** and **II-H⁺** (8.8 and 12.8 kcal/mol), the magnitude of proton brake in **1** (2.1 kcal/mol) decreased in comparison with that of **II** (4.0 kcal/mol).

Figure 3. VT-NMR chart of two Me groups in **1** and **1-H⁺** in toluene-*d*₈ and the rotational barriers around N-(*i*-Pr)Ph bond.

In (2,6-dimethylpyridin-4-yl)-2-*iso*-propylaniline **2**, two hydrogens (and two Me groups) on pyridine ring and two Me groups of *iso*-Pr in aniline **2** showed equivalent NMR signals at rt in toluene-*d*₈, while the addition of MeSO₃H (1.3 equiv) to **2** resulted in the formation of non-equivalent hydrogen signals (Figure 4). The non-equivalency of pyridinium hydrogens and *i*-Pr Me groups should be due to the rotational restriction around N-pyridinium bond and N-(*i*-Pr)Ph bond, respectively.⁸ Especially, for two hydrogens on pyridinium ring, a significant difference of the chemical shift was observed ($\Delta\delta = 1.15$ ppm). This may indicate that pyridinium ring and *iso*-Pr-phenyl ring in **2-H⁺** are co-planar and perpendicular, respectively, toward the nitrogen plane [Me-N-C₄(Py)-C₁(*i*-Pr)Ph plane]. It results that the two hydrogens (H_b: $\delta = 5.45$ ppm, H_a: $\delta = 6.50$ ppm) on pyridinium ring are located inside and outside of the *iso*-Pr-phenyl ring cone, respectively. In proton free **2**, since the rotation around N-pyridyl bond frequently occurs, the two hydrogens on the pyridine gave a single signal at average chemical shift (ca. 6.0 ppm) between H_a and H_b.

Figure 4. ^1H -NMR signals of **2** and **2-H⁺** in toluene- d_8 at rt.

VT-NMR experiment of **2** and **2-H⁺** and the line-shape simulation were subsequently performed (Figure 5). In aniline **2** in toluene- d_8 , equivalent hydrogens of pyridine ring and *i*-Pr group at 300 K were changed to non-equivalent hydrogens around 240 K and 270 K, respectively, and the rotational barriers around N-pyridyl and N-(*i*-Pr)Ph bonds were evaluated to be 11.6 and 15.5 kcal/mol, respectively. The barrier about N-(*i*-Pr)Ph bond in 4-pyridyl derivative **2** is similar to that in 2-pyridyl derivative **1** (15.1 kcal/mol).

For non-equivalent hydrogens of pyridinium ring and *i*-Pr group in **2-H⁺**, the broadening and sharpening of NMR signals were observed, respectively, with increasing temperature, while two Me signals of *i*-Pr were slightly broadened at 370 K.⁹ Full coalescence of these non-equivalent signals was not attained even at 370 K (limited heating temperature of toluene- d_8), indicating high rotational barriers for these N-Ar bonds. Nevertheless, the rotational barrier of the N-pyridinium bond in **2-H⁺** was evaluated to be 17.3 kcal/mol through the line-shape simulation, and this value was 5.7 kcal/mol higher than that in **2**. The 5.7 kcal/mol corresponds to the neat proton brake affecting the pyridine motif rotation on going from **2** to **2-H⁺**. For N-(*i*-Pr)Ph bond in **2-H⁺**, the rotational barrier could be evaluated

by the line-shape simulation of the doublet signal at the limit temperature (370K). The rotational barrier was revealed to be 21.0 kcal/mol which is 5.5 kcal/mol higher than that in **2**. This value (5.5 kcal/mol) corresponds to the neat relayed brake affecting the N-(*i*-Pr)Ph bond rotation on going from **2** to **2-H⁺**. It is noteworthy that the magnitude of proton brake around N-(*i*-Pr)Ph bond in 4-pyridyl derivative **2** (5.5 kcal/mol) is considerably larger than that in 2-pyridyl derivative **1** (2.1 kcal/mol), while the reason is unclear at the present time.

Figure 5. VT-NMR chart of hydrogens on pyridine ring and Me hydrogens in **2** and **2-H⁺** in toluene- d_8 .

VT-NMR measurement of **2** and **2-H⁺** in DMSO- d_6 followed by the line-shape simulation were also performed. The high melting point of DMSO- d_6 did not allow the determination of the barrier for the N-pyridine bond in **2** but the three other barriers around N-(*i*-Pr)Ph ($\Delta G^\ddagger = 15.3$ kcal/mol) bond in **2**, N-

pyridinium bond ($\Delta G^\ddagger = 17.2$ kcal/mol) in **2-H**⁺ and N-(*i*-Pr)Ph bond ($\Delta G^\ddagger = 21.4$ kcal/mol) in **2-H**⁺ were nicely evaluated thank to the higher range of attainable temperatures. They all were very slightly higher (0.4 kcal/mol) than those determined in toluene-*d*₈ revealing a very weak solvent effect (see SI). Furthermore, the similarity of the barriers in a weakly dissociating solvent such as toluene-*d*₈ and a strongly dissociating solvent such as DMSO-*d*₆ clearly shows that the barriers evolve from the same molecular entities in the two solvents. A conjectural contribution of ion pairs or H-bonded complexes in barrier determination for **2-H**⁺ in toluene-*d*₈ can be ruled out. In summary, going from **2** to **2-H**⁺, the rotation rates around two N-C axes are considerably decelerated by a single protonation.

The significant double brakes observed in 4-pyridyl derivative **2** may be rationalized in accordance with Figure 6. The addition of MeSO₃H to **2** leads to a selective protonation of the pyridine nitrogen to generate **2-H**⁺. In **2-H**⁺, the double bond character about an N-pyridinium bond is increased by strong resonance of the lone electron pair on *tert*-amino group with pyridinium ring, leading to the significant increase in the rotational barrier. The rotational brake around N-pyridinium bond also remarkably influences the rotation around an N-(*i*-Pr)Ph bond. We previously reported the rotational mechanism around N-Ar bond in *N*-(4-aminophenyl)-2-substituted-anilines based on DFT calculation.³ It indicates that in the transition state during N-Ar(2-substituted-phenyl) bond rotation, 4-aminophenyl group is largely twisted because of the alleviation of the steric repulsion with an *ortho*-substituent on 2-substituted-phenyl group. Similarly, the twisting of pyridyl group would be required for N-(*i*-Pr)Ph bond rotation in **2** and **2-H**⁺. The energy for the twisting of pyridinium group in **2-H**⁺ should be higher than that of pyridyl group in **2** due to the increase in the double bond character of N-pyridinium bond in **2-H**⁺. As a result, the rotational barrier around N-(*i*-Pr)Ph bond in **2-H**⁺ is significantly increased. In such interlocking controlled rotational mechanism, the change in rotational barriers around N-(*i*-Pr)Ph bond may be determined by the change in barrier for N-pyridyl bond rotation. Namely, the proton brake

in N-(*i*-Pr)Ph and N-pyridyl bonds would possess a similar magnitude. Indeed, the brake magnitude of N-(*i*-Pr)Ph bond (5.5 kcal/mol) was very close to that of N-pyridyl bond (5.7 kcal/mol).

Figure 6. Transition state model for the N-Ar bond rotation in **2** and **2-H⁺**.

CONCLUSION

We succeeded in the development of proton brake molecules through the protonation of *N*-methyl-2-*iso*-propylanilines bearing a 2- or 4-pyridyl group on the nitrogen atom. The brake magnitude in 4-pyridyl derivative was more considerable than that of 2-pyridyl derivative. Furthermore, in 4-pyridyl derivative, it was found that the rotation rates around two N-Ar bonds are remarkably decelerated by a single protonation. The deceleration of two N-Ar bond rotations proceeds via a relayed mechanism in which the brake of an N-Ar (N-pyridyl) bond also causes the brake of another N-Ar [N-(*i*-Pr)Ph] bond.¹⁰ To the best of our knowledge, this work is the first example on communicating molecular brakes. This brake system is similar to that of a penny farthing bike in which the rotational speeds of two wheels having different size (different rotational barriers) are synchronously decreased by a single front brake (Figure 1).¹¹

EXPERIMENTAL SECTION

^1H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer. In ^1H and ^{13}C NMR spectra, chemical shifts were expressed in δ (ppm) downfield from CHCl_3 (7.26 ppm) and CDCl_3 (77.0 ppm), respectively. HRMS were recorded on a double focusing magnetic sector mass spectrometer using electron impact ionization. Column chromatography was performed on silica gel (75-150 mm).

***N*-Methyl-*N*-(2-pyridyl)-2-*iso*-propylaniline (1).** Under N_2 atmosphere, $\text{Pd}(\text{OAc})_2$ (9 mg, 0.04 mmol) and *rac*-BINAP (50 mg, 0.08 mmol) in toluene (0.5 mL) were stirred for 10 min at rt. 2-*iso*-Propylaniline (135 mg, 1.0 mmol) in toluene (1.5 mL), *t*-BuONa (144 mg, 1.5 mmol) and 2-bromopyridine (98 μL , 1.0 mmol) were added to the reaction mixture, and the mixture was stirred for 3 h at 80 $^\circ\text{C}$ (oil bath). The mixture was poured into saturated aqueous NH_4Cl solution and extracted with AcOEt. The AcOEt extracts were washed with brine, dried over Na_2SO_4 , and evaporated to dryness. Purification of the residue by column chromatography (hexane/AcOEt = 10) gave *N*-(2-pyridyl)-2-*iso*-propylaniline (172 mg). Under N_2 atmosphere, to NaH (60% assay, 65 mg, 1.6 mmol) in 1,4-dioxane (2.0 mL) were added *N*-(2-pyridyl)-2-*iso*-propylaniline (172 mg, 0.8 mmol) and iodomethane (76 μL , 1.2 mmol), and then the mixture was stirred for 24 h at 80 $^\circ\text{C}$ (oil bath). The mixture was poured into saturated aqueous NH_4Cl solution and extracted with AcOEt. The AcOEt extracts were washed with brine, dried over Na_2SO_4 , and evaporated to dryness. Purification of the residue by column chromatography (AcOEt/MeOH = 4) gave **1** (159 mg, 70%). **1**: colorless oil; IR (neat) 2963 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ : 8.21 (1H, dt, J = 5.0, 1.0 Hz), 7.42 (1H, dd, J = 7.8, 1.8 Hz), 7.34 (1H, td, J = 7.6, 1.4 Hz), 7.22-7.28 (2H, m), 7.13 (1H, dd, J = 7.8, 1.4 Hz), 6.55 (1H, ddd, J = 7.8, 5.0, 0.9 Hz), 6.02 (1H, d, J = 8.7 Hz), 3.38 (3H, s), 3.04 (1H, sept, J = 6.8 Hz), 1.15 (6H, brd); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ : 159.1, 147.6, 147.5, 143.5, 136.5, 128.8, 127.9, 127.6, 127.3, 112.0, 108.2, 38.3, 27.6, 24.2, 23.6; MS (m/z) 227 (MH^+); HRMS (ESI) m/z : $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{15}\text{H}_{19}\text{N}_2$ 227.1548; found: 227.1560.

***N*-Methyl-*N*-(2,6-dimethylpyridin-4-yl)-2-*iso*-propylaniline (2).** Under N₂ atmosphere, Pd(OAc)₂ (9 mg, 0.04 mmol) and *rac*-BINAP (50 mg, 0.08 mmol) in toluene (0.5 mL) were stirred for 10 min at rt. 2-*iso*-Propylaniline (135 mg, 1.0 mmol) in toluene (1.0 mL), *t*-BuONa (144 mg, 1.5 mmol) and 4-bromo-2,6-dimethylpyridine (186 mg, 1.0 mmol) in toluene (1.0 mL) were added to the reaction mixture, and the mixture was stirred for 3 h at 110 °C (oil bath). The mixture was poured into saturated aqueous NaHCO₃ solution and extracted with AcOEt. The AcOEt extracts were washed with brine, dried over Na₂SO₄, and evaporated to dryness. Purification of the residue by column chromatography (AcOEt/MeOH = 4) gave *N*-(2,6-dimethylpyridin-4-yl)-2-*iso*-propylaniline (240 mg). Under N₂ atmosphere, to NaH (60% assay, 65 mg, 1.6 mmol) in DMF (2.0 mL) were added *N*-(2,6-dimethylpyridin-4-yl)-2-*iso*-propylaniline (240 mg, 1.0 mmol) and iodomethane (75 µL, 1.2 mmol), and then the mixture was stirred for 24 h at rt. The mixture was poured into saturated aqueous NaHCO₃ solution and extracted with AcOEt. The AcOEt extracts were washed with brine, dried over Na₂SO₄, and evaporated to dryness. Purification of the residue by column chromatography (AcOEt/MeOH = 4) gave **2** (224 mg, 88%). **2**: colorless oil; IR (neat) 2961 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 7.42 (1H, dd, *J* = 7.8, 1.8 Hz), 7.36 (1H, td, *J* = 7.4, 1.1 Hz), 7.27 (1H, td, *J* = 7.4, 1.6 Hz), 7.05 (1H, dd, *J* = 7.8, 0.9 Hz), 6.03 (2H, brs), 3.22 (3H, s), 2.89 (1H, sept, *J* = 6.8 Hz), 2.37 (6H, s), 1.14 (3H, d, *J* = 6.4 Hz), 1.10 (3H, d, *J* = 6.8 Hz); ¹³C{¹H} NMR (100 MHz, CDCl₃) δ: 157.3, 152.2, 147.2, 143.3, 128.4, 128.1, 127.5, 127.3, 103.8, 39.2, 27.7, 24.5, 24.3, 23.4; MS (*m/z*) 277 (MNa⁺); HRMS (ESI) *m/z*: [M + Na]⁺ calcd for C₁₇H₂₂N₂Na 277.1681; found, 277.1677.

***N*-Methyl-*N*-(2-pyridinium)-2-*iso*-propylaniline methane sulfonate (1-H⁺).** To **1** in CDCl₃ was added 1.3 equivalent of MeSO₃H and the ¹H-NMR was measured at rt. **1-H⁺**: ¹H NMR (400 MHz, CDCl₃) δ: 8.46 (1H, t, *J* = 5.5 Hz), 7.63 (1H, t, *J* = 7.8 Hz), 7.45-7.51 (2H, m), 7.35 (1H, m), 7.10 (1H, d, *J* = 7.8 Hz), 6.86 (1H, t, *J* = 6.4 Hz), 6.31 (1H, d, *J* = 8.7 Hz), 3.65 (3H, s), 2.92 (3H, s), 2.79 (1H, sept, *J* = 6.8 Hz), 1.23 (3H, d, *J* = 6.9 Hz), 1.11 (3H, d, *J* = 6.9 Hz). ¹³C{¹H} NMR (100 MHz, CDCl₃) δ: 152.8, 146.0, 142.6, 139.3, 137.9, 130.3, 128.6, 128.3, 127.3, 112.6, 40.6, 39.3, 28.0, 24.1, 23.6.

***N*-Methyl-*N*-(2,6-dimethylpyridinium-4-yl)-2-*iso*-propylaniline methane sulfonate (2-H⁺).** To 1 in CDCl₃ was added 1.2 equivalent of MeSO₃H and the ¹H-NMR was measured at rt. ¹H NMR (400 MHz, CDCl₃) δ: 7.44-7.50 (2H, m), 7.35 (1H, m), 7.04 (1H, dd, *J* = 7.3, 1.2 Hz), 6.55 (1H, s), 5.75 (1H, s), 3.38 (3H, s), 3.22 (3H, s), 2.90 (3H, s), 2.73 (1H, m), 2.46 (3H, s), 1.22 (3H, d, *J* = 6.7 Hz), 1.11 (3H, d, *J* = 6.7 Hz). ¹³C{¹H} NMR (100 MHz, CDCl₃) δ: 158.0, 152.7, 151.0, 145.8, 140.5, 129.9, 128.4, 128.1, 127.1, 106.3, 103.7, 40.3, 39.5, 28.0, 24.2, 23.6, 19.9, 19.4.

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Notes

The authors declare no competing financial interest.

SUPPORTING INFORMATION

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Copies of ^1H and ^{13}C -NMR spectra, VT-NMR data and the determination of the rotational barriers in **1**, **2**, **1-H⁺**, **2-H⁺**.

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REFERENCES

1. Typical papers on molecular rotors: (a) Iwamura, H.; Mislow, K. Stereochemical Consequences of Dynamic Gearing. *Acc. Chem. Res.* **1988**, *21*, 175. (b) Kelly, T. R.; Silva, H.; Silva, R. Unidirectional Rotary Motion in a Molecular System. *Nature* **1999**, *401*, 150. (c) Koumura, N.; Zijlstra, R. W. J.; van Delden, R. A.; Harada, N.; Feringa, B. L. Light-driven Monodirectional Molecular Rotor. *Nature* **1999**, *401*, 152. (d) Kottas, G. S.; Clarke, L. I.; Horinek, D.; Michl, J. Artificial Molecular Rotors. *Chem. Rev.* **2005**, *105*, 1281. (e) Coskun, A.; Banaszak, M.; Astumian, R. D.; Stoddart, J. F.; Grzybowski, B. A. Great Expectations: Can Artificial Molecular Machines Deliver on Their Promise? *Chem. Soc. Rev.* **2012**, *41*, 19.
2. Typical papers on molecular brake: (a) Kelly, T. R.; Bowyer, M. C.; Bhaskar, K. V.; Bebbington, D.; Garcia, A.; Lang, F.; Kim, M. H.; Jette, M. P. A Molecular Brake. *J. Am. Chem. Soc.* **1994**, *116*, 3657. (b) Takeuchi, M.; Imada, T.; Shinkai, S. A Strong Positive Allosteric Effect in the Molecular Recognition of Dicarboxylic Acids by a Cerium(IV) Bis[tetrakis(4-pyridyl)porphyrinate] Double Decker. *Angew. Chem. Int. Ed.* **1998**, *37*, 2096. (c) Jog, P.; Brown, R.; Bates, D. A Redox-Mediated Molecular Brake: Dynamic NMR Study of 2-[2-(Methylthio)phenyl]isoindolin-1-one and S-Oxidized Counterparts. *J. Org. Chem.* **2003**, *68*, 8240. (d) Harrington, L. E.; Cahill, L. S.; McGlinchey, M. J. Toward an Organometallic Molecular Brake with a Metal Foot Pedal: Synthesis, Dynamic Behavior, and X-ray Crystal Structure of [(9-Indenyl)tritycene]chromium Tricarbonyl. *Organometallics*, **2004**, *12*, 2884. (e)

- Yang, J.; Huang, Y.; Ho, J.; Sun, W.; Huang, H.; Lin, Y.; Huang, H.; Huang, S.; Lu, H.; Chao, I. A Pentiptycene-Derived Light-Driven Molecular Brake. *Org. Lett.* **2008**, *11*, 2279. (f) Hirose, K.; Ishibashi, K.; Shiba, H.; Doi, Y.; Tobe, Y. Highly Effective and Reversible Control of the Rocking Rates of Rotaxanes by Changes to the Size of Stimulus-Responsive Ring Components. *Chem. Eur. J.* **2008**, *14*, 5803. (g) Basheer, M. C.; Oka, Y.; Mathews, M.; Tamaoki, N. A Light-Controlled Molecular Brake with Complete ON-OFF Rotation. *Chem. Eur. J.* **2010**, *16*, 3489.
3. Iwasaki, Y.; Morisawa, R.; Yokojima, S.; Hasegawa, H.; Roussel, C.; Vanthuyne, N.; Caytan, E.; Kitagawa, O. N-C Axially Chiral Anilines: Electronic Effect on Barrier to Rotation and A Remote Proton Brake. *Chem. Eur. J.* **2018**, *24*, 4453.
4. Typical papers on molecular rotors based on the control of N-C bond rotation: (a) Dial, B. E.; Rasberry, R. D.; Bullock, B. N.; Smith, M. D.; Pellechia, P. J.; Profeta, S, Jr.; Shimizu, K. D. Guest-Accelerated Molecular Rotor. *Org. Lett.* **2011**, *13*, 244. (b) Dial, B. E.; Pellechia, P. J.; Smith, M. D.; Shimizu, K. D. Proton Grease: An Acid Accelerated Molecular Rotor. *J. Am. Chem. Soc.* **2012**, *134*, 3675. (c) Wu, Y.; Wang, G.; Li, Q.; Xiang, J.; Jiang, H.; Wang, Y. A multistage rotational speed changing molecular rotor regulated by pH and metal cations. *Nat. Commun.* **2018**, *9*, 1953.
5. Although the aromatic nucleophilic substitution of 2-*iso*-propylaniline with 4-bromo-pyridine hydrochloride gave the desired *N*-(4-pyridyl)-2-*iso*-propylaniline, the chemical yield was poor.
6. (a) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. A Simple Catalytic Method for the Conversion of Aryl Bromides to Arylamines. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1348. (b) Hartwig, J. F.; Loue, J. Palladium-catalyzed synthesis of arylamines from aryl halides. Mechanistic studies lead to coupling in the absence of tin reagents. *Tetrahedron Lett.* **1995**, *36*, 3609.

- 1
2
3 7. (a) C. Wolf, *Dynamic Stereochemistry of Chiral Compounds: Principles and Applications*, RSC
4 Publishing: Cambridge, 2008. (b) Clayden, J.; Fletcher, S. P.; McDouall, J. J. W.; Rowbottom, S.
5 J. M. Controlling Axial Conformation in 2-Arylpyridines and 1-Arylisoquinolines: Application
6 to the Asymmetric Synthesis of QUINAP by Dynamic Thermodynamic Resolution. *J. Am. Chem.*
7 *Soc.* **2009**, *131*, 5331.
8
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15 8. Although the rotational brake around N-pyridinium bond in **1-H⁺** may also occur, it was difficult
16 to detect in the 2-pyridyl substrates having no equivalent hydrogens such as 4-pyridyl derivative
17 **2-H⁺**. On the other hand, in 4-aminophenyl derivative **II**, the non-equivalency of hydrogens on
18 4-aminophenyl ring was not observed through the addition of MeSO₃H because of the low
19 rotational barrier around N-(4-NH₃⁺Ph) bond.
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26 9. The broadened signals of Me groups at low temperature may result from the physical state of the
27 solution.
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31 10. One may augur that the oxidation or methylation at the pyridine nitrogen in **2** to yield the
32 corresponding N-oxide or N-methyl-pyridinium salt would also produce a strong deceleration of
33 the rotation rates. These chemical transformations which do not comply with the reversibility
34 requirement in molecular motor brake were not further considered.
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40 11. A reviewer suggested that bevel gear bearing two orthogonal rotors is more appropriate than the
41 penny farthing bike as a mechanical analogy. This is right in terms of topology but the gear
42 analogy is somewhat misleading for our two blade molecular machine. The penny farthing bike
43 is another example in which two interdependent rotating systems with different rotation rates can
44 be simultaneously affected by a single brake.
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