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COMPUTATIONAL STUDIES ON THE RACEMIZATION BARRIERS OF WINDING VINE-SHAPED HETEROBIARYLS WITH MOLECULAR ASYMMETRY[‡]

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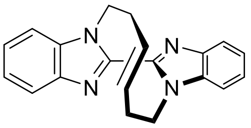
[‡]This paper is dedicated to Professor Tohru Fukuyama on celebration of his 70th birthday.

Abstract – DFT calculation studies were performed for the estimation of racemization barrier of winding vine-shaped heterobiaryls showing molecular asymmetry. The calculated value showed good agreement compared with that derived from experimental studies. Effects of hetroaromatic structure, carbon-carbon double bond at the winding-vine moiety, substituent at the double bond, and substituent at the heteroaromatic rings were studied.

INTRODUCTION

Design of topologically interesting organic molecules is of considerable interest in organic chemistry.[1] Such compounds showing molecular asymmetry also attract attention since potential application of its chirality toward asymmetric catalysis, liquid crystals, molecular recognition, etc.[2] We have recently reported that preparation of heterobiaryl derivatives bearing a linkage composed of a certain number of alkenylene chain, was successfully achieved by ruthenium-catalyzed ring-closing metathesis.[3] The thus obtained compounds **1** and **2** exhibited chiralities despite possessing no carbogenic asymmetric



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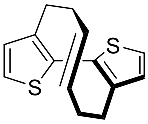

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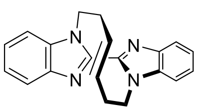
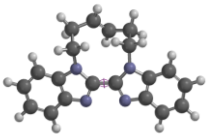
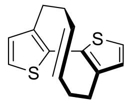
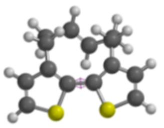
stereocenter. Such a unique compound was named as *winding vine-shaped molecular asymmetry* that showed axial, planer, and helical chiralities in the molecule. We have also been successful to obtain vine-shaped compounds in an enantimomerically enriched manner by either optical resolution with a chiral column,[4,5] enantioselective synthesis by asymmetric metathesis,[6] or (dynamic) kinetic resolution.[7] Synthetic protocols to obtain enantioenriched **1** and **2** enabled us to study racemization behaviors of these compounds and found that a harsh condition was required for the racemization of imidazole derivative **1**, while bithiophene **2** was slowly racemized even at room temperature.[8,9] Our concern turned to the understanding of the relationship of the molecular structure of winding vine-shaped heterobiaryls with the racemization behavior. Nevertheless, it remains difficulties to design structures of significant interest but involves problems on energetic stability as well as establishing practical synthetic pathway. Herein, we describe computational studies on the racemization behaviors of winding vine-shaped heterobiaryls and the calculated energy values are compared with the corresponding data evaluated by experimental studies.[10]

RESULTS AND DISCUSSION

Racemization barrier was evaluated by DFT calculation of B3LYP/6-31G*.[11,12] The initial geometry of **1** was based on the result of X-ray crystal structure analysis of **1**[8] and **2**.[9] The structure of the racemization transition state **1'** and **2'**, which conformations involve dihedral angle between two heteroaromatic moiety is 0°.[13] As summarized in Table 1, the energy of bisbenzoimidazole **1** was calculated as −992.00877 and

Table 1. Experimental and calculation results for the racemization barrier of winding vine-shaped heterobiaryl **1** and **2**[a]

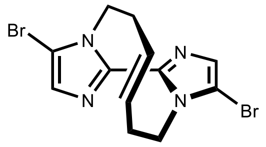
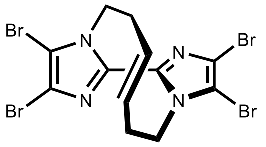
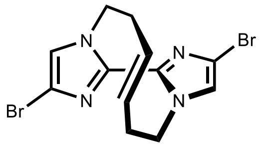
heterobiaryl	energy[b] au	transition state	energy[c] au	calculation $kJmol^{-1}$	experimental $kJmol^{-1}$
 **1**	−992.00877	 **1'**	−991.95598	138.59	130.15
 **2**	−1338.27096	 **2'**	−1338.23053	106.15	101.69

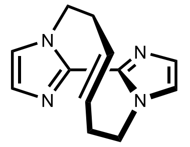
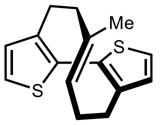
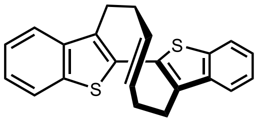
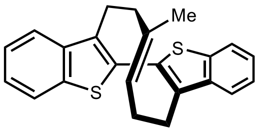
[a] DFT calculation by B3LYP/6-31G*. [b] Geometry based on the results of X-ray crystal structure analysis was employed (ref 4 and 9). [c] The initial structure where dihedral angle of Nsp^2−C−C−Nsp^2 (**1'**) or S−C−C−S (**2'**) is set as 0°.

that of bithiophene **2** was −1338.27096 au. The energy value of **1'** and **2'** was also estimated as −991.95598 and −1338.23053 au, respectively, and the energy difference between **1** and **1'**/**2** and **2'** was 138.59 kJmol^{-1} and 106.15 kJmol^{-1}, respectively. These calculated energies showed close values based on the experimental studies for **1** and **2** (130.15 and 101.69 kJmol^{-1}, respectively).

We have also shown that racemization behaviors of bisimidazole derivatives bearing a bromine substituent at the 4,4'-positions and/or 5,5'-positions and bithiophene and benzobithiophene derivatives bearing a methyl substituent at the carbon−carbon double bond on the winding-vine moiety.[8] We have learned that dibrominated bisimidazole bearing bromine atomes at the 5,5'-positions **3** and tetrabrominated derivative **4** showed higher energy than that of 4,4'-dibromobisimidazole **5**. The results suggest that a substituent at the 5,5'-positions effectively improved the racemization barrier, while little effect by the bromine atom at the 4,4'-positions. The calculation studies also supported the experimental results to observe similar values in each bisimidazole derivatives. It was also found that unsubstituted bisimidazole, whose experimental study has not been achieved because of difficulties in the isolation of the enantiomer by HPLC with a chiral column, showed similar calculation result (120.83 kJmol^{-1}). We have also found that a methyl substituent at the carbon−carbon double bond at the winding-vine moiety in bithiophene improved the racemization barrier effectively,[9] however, these results did not support the calculation study to observe small difference by the introduction of the substituent.

Table 2. Experimental and calculation results for the racemization barrier of winding vine-shaped bisimidazoles and bithiophenes[a]

heterobiaryl		calculation kJmol^{-1}	experimental kJmol^{-1}
	**3**	139.36	134.65
	**4**	139.41	140.04
	**5**	123.01	126.56

	**6**	120.83	–[b]
2		106.15	101.69
	**7**	105.44	–[c]
	**8**	114.16	97.51
	**9**	112.03	109.89

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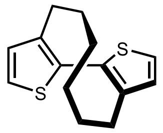
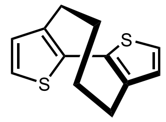
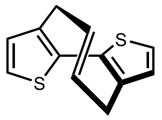
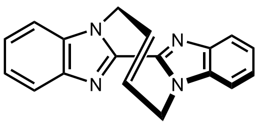
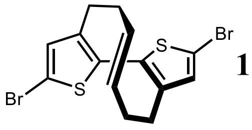
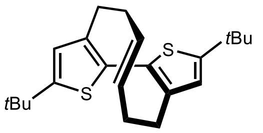
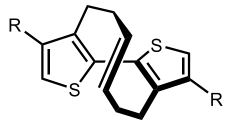
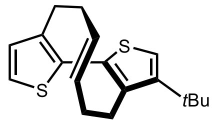
[a] DFT calculation by B3LYP/6-31G*. [b] The experimental result is not available because of difficulties in the separation of the enantiomer. [c] Little racemization was observed experimentally suggesting high racemization barrier.

Although it is of our particular concern on the effect of the carbon−carbon double bond at the winding-vine moiety toward the racemization behavior, it has not been achieved to estimate the racemization barrier experimentally because of analytical difficulties of the related derivative, where the double bond is reduced to the corresponding single bond. Calculation of bithiophene **10** revealed to show 32.61 kJmol^{-1}, which was found to be ca. 70 kJmol^{-1} lower than the olefinic analog **2**. The result suggests that it is indeed important to possess a double bond at the winding-vine moiety in heterobiaryls. We have also performed DFT calculation of a bithiophene derivative bearing shorter alkylene chain length. Bithiophene composed of 8-membered ring **11** showed a similar value 36.99 kJmol^{-1} to that of **10**. It was also found that 8-membered thiophene and benzoimidazole derivatives bearing *E*-olefin **12** and **13**, which syntheses were shown to be unsuccessful experimentally,[4] also exhibited small barriers (18.04 kJmol^{-1} and 26.98 kJmol^{-1}, respectively) probably because of much higher ring strain of the *E*-olefin in the anti-conformation of bithiophene.

The substituent of bithiophene ring would also be of structural interest concerning the racemization behavior, however, such studies have not been performed experimentally because of synthetic difficulties in the introduction of substituents into the thiophene rings of **2**. It was found that a brominated derivative at the 5,5'-positions showed little effect compared with unsubstituted bithiophene **2** (101.69 kJmol^{-1}).

Further bulky group at the 5,5'-positions was also found to hardly improve the barrier (**15** = 101.27 kJmol^{-1}). By contrast, dibromobithiophene substituted at the 4,4'-positions **16a** showed much higher energy (120.69 kJmol^{-1}). Bithiophenes bearing the related dichloro derivative also showed simmilar effect whereas fluorine-substituted bithiophene **16c** showed little difference from **2** (R = H). It was revealed that an alkyl or aryl substituent also showed higher barriers (**16d** and **16e**) and 4,4'-di-*tert*-butylated bithiophene **16f** indicated the highest value (141.36 kJmol^{-1}). A partially substituted with the *tert*-butyl group was also found to show the significantly improved racemization barrier (136.74 kJmol^{-1} in **17**). These results are summarized in Table 3.

Table 3. DFT Calculation results for the racemization barrier of winding vine-shaped bisimidazoles and bithiophenes[a]

heterobiaryl	calculation[b] kJmol^{-1}	heterobiaryl	calculation[b] kJmol^{-1}
 **10**	32.61	 **11**	36.99
 **12**	18.04	 **13**	26.98
 **14**	106.91	 **15**	101.27
 **16**	**16a** (R = Br): 120.69 **16b** (R = Cl): 118.20 **16c** (R = F): 103.05 **16d** (R = Me): 114.47 **16e** (R = Ph): 121.85 **16f** (R = ^{t}Bu): 141.36	 **17**	136.74

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[a] DFT calculation by B3LYP/6-31G*. [b] The calculated value of the racemization barrier.

Our further concern is turned to the effect of sulfur atom toward racemization. A high racemization barrier was observed when the sulfur atom was oxidized to the corresponding sulfone. The energy of **18** (127.81 kJmol^{-1}) was imporved ca. 21 kJmol^{-1} compared with the related dibromobithiophene **14**. A biphenyl analog **19** was also calculated to show 211.56 kJmol^{-1} (Chart 1) whereas synthesis of **19** or a related derivative by ring-closing metathesis has not been achieved to date.[14]

18 (Z = SO_2): 127.81 kJmol^{-1}

14 (Z = S): 106.91 kJmol^{-1}

19: 211.56 kJmol^{-1}

Chart 1. Racemization barrier of winding vine-shaped (hetero)biaryls **18** and **19**

In conclusion, we have performed calculation studies on the racemization behaviors of winding vine-shaped heterobiaryls showing molecular asymmetry. A part of derivatives described here, indeed, involves difficulties in the synthesis of the structure and/or in the actual separation by HPLC with a chiral column and thus the racemization barrier has not been evaluated experimentally. However, computational studies on the caluculation of racemization barrier achieved to estimate such energy values resulting that substituents at the 4,4'-positions of thiophene, 5,5'-positions of imidazole, *E*- or trisubstituted olefinic moiety at the vine moiety, and oxidation of sulfur of the thiophene ring are remarkably effective for the improved racemization barrier. The findings would be highly helpful for the design of a new class of structures exhibiting winding vine-shaped molecular asymmetry.

CALCULATION

Computational studies were carried out employing SPARTAN version 13 and 16 as a calculation software. The racemization barrier was evaluated by DFT calculation according to Becke's three-parameter hybrid method with LYP correlation with basis set of 6-31G* (B3LYP/6-31G*).[11,12] The energy values of all structures represent those of the HOMO level.[15]

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

1. E. L. Eliel, S. H. Wilen, and M. P. Doyle, 'Basic Organic Stereochemistry', Wiley, New York, 2001, pp. 608-648; R. Adams and H. C. Yuan, *Chem. Rev.*, 1933, **12**, 261.
2. R. Noyori, *Angew. Chem. Int. Ed.*, 2002, **41**, 2008; R. Noyori and H. Takaya, *Acc. Chem. Res.*, 1990, **23**, 345.
3. R. H. Grubbs, *Adv. Synth. Catal.*, 2007, **349**, 34; P. Schwab, M. B. France, J. W. Ziller, and R. H. Grubbs, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2039; C. W. Bielawski and R. H. Grubbs, *Angew. Chem. Int. Ed.*, 2000, **39**, 2903.
4. S. Nishio, T. Somete, A. Sugie, T. Kobayashi, T. Yaita, and A. Mori, *Org. Lett.*, 2012, **14**, 2476; D. Monguchi, A. Yamamura, T. Fujiwara, T. Somete, and A. Mori, *Tetrahedron Lett.*, 2010, **51**, 850.
5. A. Mori, D. Matsuoka, S. Ashida, R. Inoue, K. Maruhashi, Y. Okayama, G. H. Jin, and K. Okano, *Heterocycles*, 2017, **95**, 268.
6. Y. Okayama, S. Tsuji, Y. Toyomori, A. Mori, S. Arae, W.-Y. Wu, T. Takahashi, and M. Ogasawara, *Angew. Chem. Int. Ed.*, 2015, **54**, 4927.
7. K. Maruhashi, Y. Okayama, R. Inoue, S. Ashida, Y. Toyomori, K. Okano, and A. Mori, *Sci. Rep.*, 2018, **8**, 1704.
8. Y. Okayama, K. Maruhashi, S. Tsuji, and A. Mori, *Bull. Chem. Soc. Jpn.*, 2015, **88**, 1331.
9. Y. Toyomori, S. Tsuji, S. Mitsuda, Y. Okayama, S. Ashida, A. Mori, T. Kobayashi, Y. Miyazaki, T. Yaita, S. Arae, T. Takahashi, and M. Ogasawara, *Bull. Chem. Soc. Jpn.*, 2016, **89**, 1480.
10. Preliminary results on the computational racemization studies were in part described in ref 7.
11. A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648.
12. C. Lee, W. Yang, and R. G. Parr, *Phys. Rev. B*, 1988, **37**, 785.
13. Related calculation studies on biphenyl derivatives: A. Bihlmeier, J. Rotzler, M. Rickhaus, M. Mayor, and W. Klopper, *Phys. Chem. Chem. Phys.*, 2015, **17**, 11165.
14. Attempted ring-closing metathesis resulted in giving no desired product **20**: Unpublished results in our group.
15. Details on calculation results. See Supporting Information.