

Analysis of Interconversion between Atropisomers of Chiral Substituted 9,9'-Bicarbazole

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Interconversion of atropisomers of chiral 3,3'-di-*tert*-butyl-9,9'bicarbazole linked by a single N–N bond was analyzed by DFT calculations and experiments. The calculations revealed that the *trans* transition state has a lower energy for the interconversion than the *cis* transition state. The lowest transition state of interconversion between natural dixiamycins A and B containing a 9,9'-bicarbazole structure was found to be the *trans* transition state. The calculations also indicated that degradation through N–N bond cleavage was faster than racemization. Atropisomeric enantiomers of 3,3'-di-*tert*-butyl-9,9'-bicarbazole were resolved by chiral HPLC for the first time, and then racemization and N–N bond cleavage were investigated by heating experiments, showing that racemization did not take place below the degradation temperature.

In recent years, nitrogen-containing heteroaromatic dimers with N-N bond linkages have emerged as fascinating molecules in many fields such as organic chemistry, materials chemistry, and medicinal chemistry.^[1,2] Among such heterocyclic dimers, dimers of unsymmetrical heterocycles linked by a single N-N bond can possess axis chirality depending on the rotational energy barrier (Figure 1A). To date, only two examples of resolution of such atropisomers, 2,2',5,5'-tetramethyl-1,1'-bipyrrole-3,3'-dicarboxylic acid (1)^[3] and natural antibiotic dixiamycins A (2) and B (3),^[4] have been reported (Figure 1B). The resolution of racemic bipyrrole 1 by crystallization as diastereomeric salts of brucine was achieved in 1931. However, the enantiomeric purity of 1 and the thermal stability of its chirality were not clear, since the enantiomeric purity was studied only by optical rotation. More recently, reported natural dixiamycins A (2) and B (3) are diastereomers but not enantiomers owing to the additional stereogenic centers. The reported calculated transition state for the interconversion between 2 and 3 is not consistent with that of 9,9'-bicarbazole.^[5] Given this background, in order to develop novel chiral heteroaromatic dimers with a N-N bond, it is

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Figure 1. (A) Atropisomeric enantiomers of heterocyclic dimers linked by a N–N bond. (B) Reported atropisomers, 2,2',5,5'-tetramethyl-1,1'-bipyrrole-3,3'-dicarboxylic acid (1)^[3] and dixiamycins A (2) and B (3).^[4] (C) Atropisomeric enantiomers of 3,3'-di-*tert*-butyl-9,9'-bicarbazole (4).

necessary to clarify the molecular dynamic properties of atropisomeric enantiomers of a simple heteroaromatic dimer. In this paper, we report a theoretical analysis on the interconversion between atropisomeric enantiomers of chiral 3,3'-di-*tert*butyl-9,9'-bicarbazole **4** (Figure 1C), the first resolution of enantiomers by chiral HPLC, and an experimental analysis of the racemization and degradation.

Based on a reported theoretical study of the conformation of 9,9'-bicarbazole,^[5] the stable conformation of **4** and the transition states for the interconversion between the atropisomers were calculated at the B3LYP/6-31G(d) level of theory





Figure 2. Calculated transition states for interconversion between atropisomeric enantiomers and homolytic cleavage of the N–N bond of 4.

(Figure 2). Depending on the direction of the lone pairs on the nitrogen atoms, *cis* and *trans* forms exist for the transition states (Figure 3). Due to the *tert*-butyl substituents, the *cis* and *trans* forms possess three $[(R)-cis-TS1_4, (S)-cis-TS1_4, cis-TS2_4]$ and three (*trans-TS1*₄, (*R*)-*trans-TS2*₄, (*S*)-*trans-TS2*₄) transition states, respectively. The energies of the *trans* transition states (166.9–167.0 kJ/mol) were lower than those of the *cis* transition states (200.2–200.3 kJ/mol). Therefore, the interconversion between the atropisomers of **4** takes place through the *trans* transition states of interconversion between dixiamycins A (**2**) and B (**3**) were also



Figure 3. Cis and trans transition states of 9,9'-bicarbazole.



Figure 4. Cis and trans transition states of dixiamycins.

reinvestigated (Figure 4, Figure S1). Although *cis* transition states were previously reported to have the lowest transition states (196.0–197.7 kJ/mol), the lowest transition states were revised to be the *trans* transition states (163.2–165.2 kJ/mol).

The energies of two molecules of the carbazolyl radical **5**[•] were also calculated [roB3LYP/6-31G(d)] (Figure 2), since 9,9'bicarbazole is known to undergo thermal N–N bond cleavage.^[6] The energy was calculated to be 135.3 kJ/mol, which is lower than the energies of the *trans* transition states of interconversion. Thus, the thermal degradation of the enantiomer of **4** through N–N bond cleavage is predicted to be faster than the racemization.

In order to confirm the calculation results for 4, we succeeded in resolving the enantiomers of 4 by chiral HPLC for the first time using a DAICEL CHIRALPAK IB column (hexane) (Figure 5A). The circular dichroism (CD) spectra of the enantiomers of 4 and UV-vis absorption spectrum of (\pm) -4 were recorded as shown in Figure 5B and Figure 55C. Since a single crystal to determine the absolute configuration for X-ray analysis was not obtained, the absolute configuration was assigned by TD-DFT calculations [cam-B3LYP/6-31G(d)] (Figure 5D and Figure 5E). The simulated CD and UV-vis absorption spectra showed good correlation with the experimental spectra.^[7] Judging from the sign of the simulated and experimental CD spectra, the absolute configurations of the resolved enantiomers of 4 were assigned as shown in Figure 5A and Figure 5B. To determine the degradation temperature, thermolysis of (\pm)-4 was performed. The solution of (\pm)-4 in odichlorobenzene- d_4 was heated at 120 or 140 °C and the degradation was followed by ¹H NMR spectroscopy using anisole as an internal standard. While the degradation was not observed at 120 °C, it did take place at 140 °C, and the amount of (\pm) -4 was reduced to 87% after 20 h. Based on this result, the resolved enantiomer of 4 was heated in o-dichlorobenzene at 120 or 140°C and the racemization was monitored by chiral HPLC analysis. Racemization was not observed after 20 h at either temperature. This result is consistent with the calcuCommunications doi.org/10.1002/ejoc.202001385





Figure 5. (A) Resolution of (\pm) -4 by CHIRALPAK IB (hexane). (B) CD spectra of (S)-4 and (R)-4 in hexane $(2.78 \times 10^{-5} \text{ M})$. (C) UV-vis absorption spectrum of (\pm) -4 in hexane $(1.0 \times 10^{-5} \text{ M})$. (D) Calculated CD spectrum of (S)-4 [cam-B3LYP/6-31G(d)]. The intensity of the simulated curve using a Gaussian function is magnified 50 times compared to that of the calculated bands for clarity. (E) Calculated absorption spectrum of **3**.

lations in that the racemization energy is higher than the degradation energy. Racemization of **4** does not take place below the degradation temperature.

In conclusion, DFT calculations of 3,3'-di-tert-butyl-9,9'bicarbazole 4 indicated that the *trans* transition states were the lowest transition states for the interconversion between the atropisomers. The calculated lowest transition state of interconversion between dixiamycins A and B was also revised to be the *trans* transition state. Furthermore, the calculations predicted that degradation was faster than racemization. Indeed, enantiomers of 4 were resolved by chiral HPLC for the first time, and heating experiments showed that racemization did not take place below the degradation temperature. We believe that these fundamental results obtained by a combination of theoretical and experimental methods will be useful for the creation of novel chiral heteroaromatic compounds with a N–N bond and the elucidation of their chiral properties.

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Conflict of Interest

The authors declare no conflict of interest.

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