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A Complete Gear System in *N*-Benzoyl-Carbazole Derivatives

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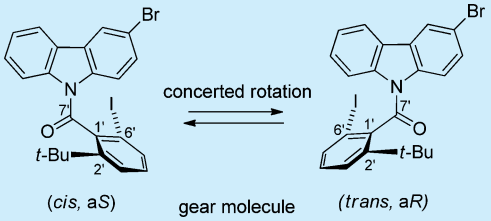
Supporting Information

ABSTRACT: 2′,6′-Disubstituted *N*-benzoylated carbazole derivatives were found to exhibit atropisomerism. The bulky substituents restricted rotation about the N−C7′ and C7′−C1′ bonds to separate four atropisomers, in which rotation about the C7′−C1′ bond was in perfect concert with rotation about the N−C7′ bond. Complete geared rotation without slippage at 37 °C for 7 days was observed for the first time. Conformational analysis clarified the preference for the gear system over other internal conversion pathways.



As part of our research on stereochemical and physicochemical analyses of biologically active molecules,[1] we reported the atropisomeric property of the 2′,6′-disubstituted indole derivatives (*N*-benzoylated 2-methylindoles) (Figure 1).[2] The isolation of each enantiomer of **1** (a*R*, a*S*) with high

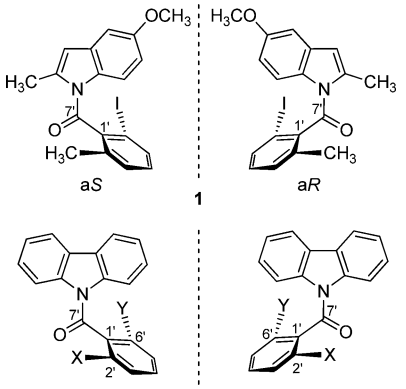


Figure 1. 2′-Iodo-6′-methylsubstituted *N*-benzoyl-indole derivative **1** and 2′,6′-disubstituted *N*-benzoyl-carbazole derivatives.

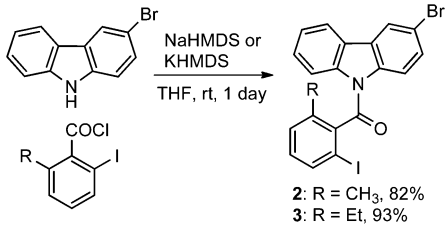
stereochemical stability confirmed that the rotation about the C7′−C1′ axis is fully restricted by substituents at C2′ and C6′ to form a twisted conformation.

In this context, our attention next focused on carbazole. Carbazoles have attracted increasing attention from medicinal chemists owing to their therapeutic value derived from carbazole alkaloids that act as antibacterial, antifungal, and antiviral agents.[3] However, no reports have considered its *N*-benzoylated structure from the viewpoint of axial chirality.

In this paper, we report the atropisomeric properties of 2′,6′-disubstituted *N*-benzoylated carbazole derivatives. It was found that the bulky substituents at the 2′- and 6′-positions of the benzoyl moiety make the N−C7′ and C7′−C1′ axes move together like a complete gear. The process by which this gear system moves was examined in detailed experimental and computational studies.

In order to estimate the steric effect at the *ortho*-positions of the benzoyl moiety on the rotation about the N−C7′ and C7′−C1′ axes, we planned to synthesize the variously 2′-alkyl-6′-iodo-substituted derivatives. Following the established method, *N*-benzoylated carbazole derivatives (**2**−**5**) were synthesized as shown in Scheme 1.[4]

Scheme 1. Preparation of 2′,6′-Disubstituted *N*-Benzoyl-carbazoles



First, *N*-(2′-iodo-6′-methylbenzoyl)-3-bromocarbazole **2** was characterized using ^{1}H NMR spectroscopy, which showed two sets of resonances corresponding to *cis* and *trans* conformations (*cis*/*trans* = 1:1.25). Because the rotational barrier of the N−C7′ axis is less than that required for the isolation of each conformer at 23 °C, compound **2** was observed as one peak on nonchiral HPLC. However, **2** was separated into two peaks when analyzed in a chiral column (CHIRALPAK IB) at 23 °C, which means that the C7′−C1′ axis was frozen as observed in indole derivative **1** (Figure 2).[2] The enantiomers of compound **2** were successfully isolated using preparative chiral HPLC with opposite $[\alpha]_D^{20}$ values: **2A** (with shorter retention time in

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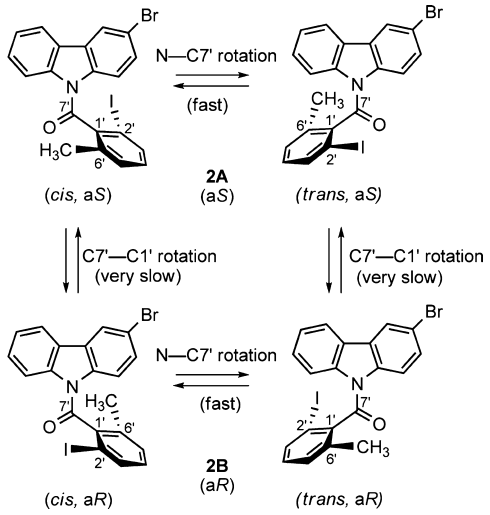

Figure 2. Interconversion path for stereoisomers of **2**.

HPLC) as 99%ee showed $[\alpha]_D^{20}$ −10.7 (*c* 0.12, $CHCl_3$), and **2B** (with longer retention time in HPLC) as 99%ee showed $[\alpha]_D^{20}$ +10.9 (*c* 0.15, $CHCl_3$). We also examined the stereochemical stability with a $\Delta G^{\ddagger}$ value of 108 kJ mol^{-1} for **2A** and **2B**.[5] The similar barrier height in compound **1** in comparison with that in *N*-(2′-iodo-6′-methylbenzoyl)-2-methylindole ($\Delta G^{\ddagger}$ value of 109 kJ mol^{-1}) is likely explained by the similar steric or electronic effect due to the methyl group vs the aromatic C−H.

We next examined carbazoles with bulkier substituents, ethyl and isopropyl groups (**3** and **4**, respectively). For both compounds, two sets of resonances corresponding to *cis* and *trans* conformations (*cis*/*trans* = 1:1.16) were observed in the ^{1}H NMR spectra, although the isolation of each diastereomer (*cis*/*trans*) on a nonchiral column failed. Separation analysis of **3** and **4** on a chiral column (CHIRALPAK IB) provided results contrary to our expectations. Compound **3** was partially separated at 23 °C, and we managed to isolate the atropisomers of **3** with opposite $[\alpha]_D^{20}$ values: **3A** (with shorter retention time in HPLC) as 99%ee showed $[\alpha]_D^{20}$ −10.2 (*c* 0.12, $CHCl_3$), and **3B** (with longer retention time in HPLC) as 92% ee showed $[\alpha]_D^{20}$ +9.5 (*c* 0.09, $CHCl_3$). The stereochemical stability with a $\Delta G^{\ddagger}$ value of 110 kJ mol^{-1} for **3A** and **3B** may account for the increased stability of the C7′−C1′ axis in **3**, although less separable peaks were observed on CHIRALPAK IB. In addition, **4** was observed as one peak on all chiral columns examined at 23 °C. Thus, we failed to isolate atropisomers of **4**. Considering the van der Waals volumes of methyl (21.6 Å^3), ethyl (38.9 Å^3), and isopropyl (56.2 Å^3) groups,[6] it appears strange that steric hindrance does not contribute to separating the atropisomers arising from the C7′−C1′ axis. Especially in compound **4**, the more hindered isopropyl group may produce an unusual effect that unfreezes the rotation about the C7′−C1′ axis, causing loss of the atropisomeric property.

Finally, amazing results were provided by *tert*-butyl-substituted compound **5**. Similar to the above-mentioned compounds **1**−**4**, two sets of resonances corresponding to *cis* and *trans* conformations were observed in the ^{1}H NMR spectrum (*cis*/*trans* = 1:1.17). However, **5** was observed as two separated peaks (**5I**, **5II**) on nonchiral HPLC, and four stereoisomers were resolved by a chiral column (CHIRALPAK IB). All the isomers were successfully isolated using preparative chiral HPLC.

For compound **5** containing the *tert*-butyl and iodo groups at the *ortho*-positions of benzoyl, rotation about the N−C7′ and C7′−C1′ axes are fully restricted, mainly due to the steric effect. In such systems, four stereoisomers can potentially result since each axis can assume two orientations (*cis*/*trans* for the N−C7′ axis, a*R*/a*S* for the C7′−C1′ axis). The chromatogram of chiral HPLC of the stereoisomers and the $[\alpha]_D$ data are shown in Figure 3. Fortunately, **5I-B** and **5II-B** could be analyzed by X-

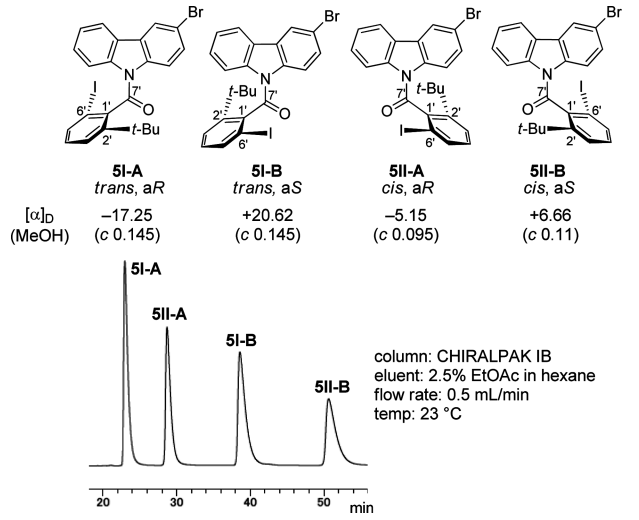

Figure 3. Separation of **5** (**5I** and **5II**) into the enantiomers (**A** and **B**) on a chiral column and $[\alpha]_D$ data measured in CH_3OH.

ray crystallography to determine the absolute stereochemistry (Figure 4).[7] **5I-B** was assigned to be (*trans*, a*S*), and **5II−B** was assigned to be (*cis*, a*S*); hence, **5I-A** was (*trans*, a*R*), and **5II-A** (*cis*, a*R*).

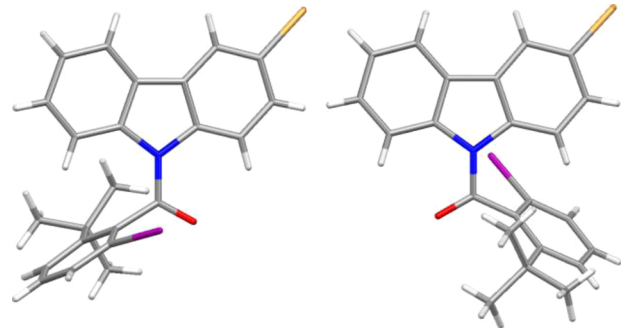

Figure 4. X-ray crystal structures of **5I-B** (left) and **5II-B** (right).

Using the enantiomerically pure stereoisomer (**5II-B**), the stereochemical stability was examined using chiral HPLC analysis at 37 °C in toluene after 9 days. We observed that **5II-B** was converted to **5I-A** with a $\Delta G^{\ddagger}$ value of 102 kJ mol^{-1}, and no interconversion between any other pair (i.e., **5II-B**/**5II-A**, **5II-B**/**5I-B**) was seen (Figure 5). Similarly, enantiomerically pure **5I-B** was converted to **5II-A** with a $\Delta G^{\ddagger}$ value of 103 kJ mol^{-1}; no interconversion between any other pair (i.e., **5I-B**/**5I-A**, **5I-B**/**5II-B**) was observed over 7 days.[8] It is clear that the rotation about the C7′−C1′ axis must be in perfect concert with the rotation about the N−C7′ axis at 37 °C for at least 7 days (Figure 6). Although such behavior has been observed in

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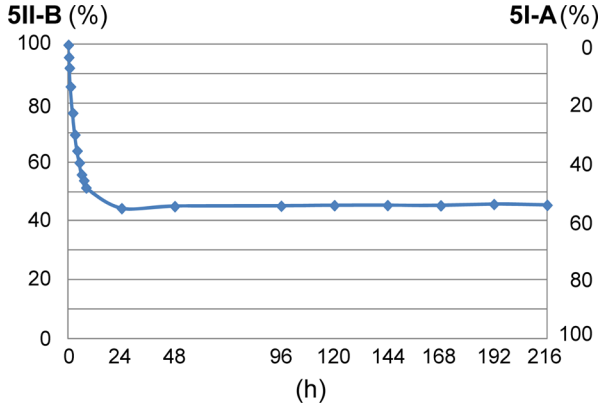

Figure 5. Conversion between **5II-B** (left) and **5I-A** (right) at 37 °C.

tertiary aromatic amide systems,[9] complete geared rotation without slippage was observed here for the first time.

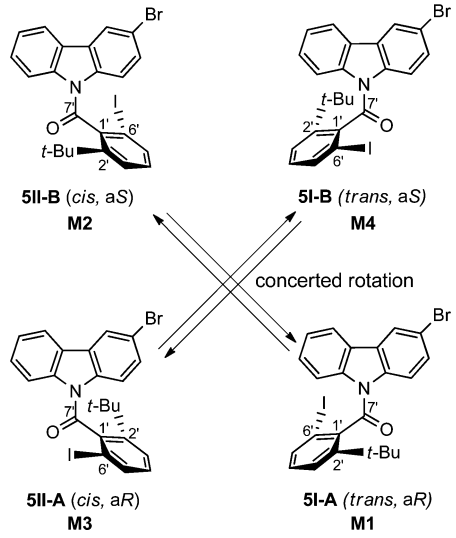

Figure 6. Interconversion path for stereoisomers of **5**.

In order to estimate the stability of this gear system, conversion of the enantiomerically pure **5II-B** to **5I-A** at higher temperature was followed by analytical HPLC until the gear slipped. In previous papers on molecular gear systems, gear slippage was observed at ambient temperature.[9] However, the slippage in this system was finally observed only after 27 h of heating at 100 °C.[10]

We next carried out *in silico* conformational analysis[11] of **5** to confirm the advantage of this geared rotation over other conversion pathways.

To obtain the initial 3D molecular coordinates of **5**, the X-ray crystal structures of **5II-B** shown in Figure 4 were used. *Ab initio* calculations were performed using the RHF/CEP-4G basis set with a Gaussian program.[12] To cover all conformational spaces, rotational steps of the single bonds in **5** were 15 degrees. As mentioned above, **5** can rotate around the N−C7′ and C7′−C1′ axes, which results in the energy surface shown in Figure 7.

There were four stable conformers (**M1**, **M2**, **M3**, and **M4**), corresponding to **5I-A**, **5II-B**, **5II-A**, and **5I-B**, respectively, as shown in Figure 6. Based on the energy barriers of the pathways on the energy surface, it is clear that the interconversion between conformers **M1** and **M2**, and between

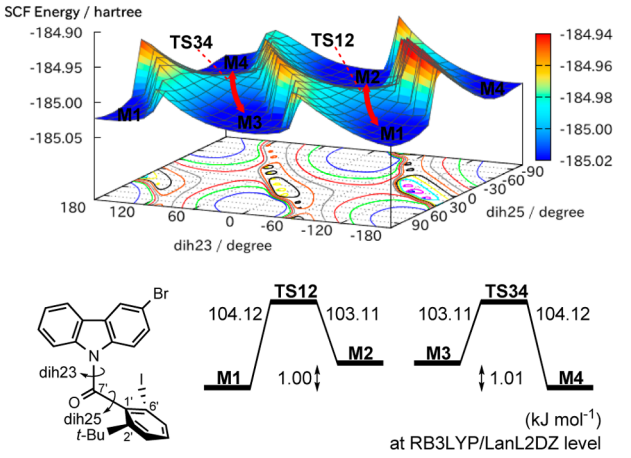

Figure 7. Energy surface for **5**.

M3 and **M4**, is easy. Furthermore, we carried out additional calculations to estimate the activation barrier of geared rotation at the RB3LYP/LanL2DZ level.[13] These results are consistent with the experimental results obtained from HPLC analysis and X-ray crystallography.

In conclusion, an atropisomeric property was found in 2′,6′-disubstituted *N*-benzoylated carbazole derivatives. The bulky *tert*-butyl group and iodo group restricted the rotation about the N−C7′ and C7′−C1′ bonds to separate the four atropisomers, in which the rotation about the C7′−C1′ bond is in perfect concert with the rotation about the N−C7′ bond. The process by which this molecular gear system starts moving was investigated by comparison with the stereochemical properties of variously 2′,6′-disubstituted *N*-benzoylated carbazole derivatives. Furthermore, conformational analysis clarified the preference for the gear system over other internal conversion pathways. Although we have only limited information on this molecular gear system, we hope that this study will contribute to elucidating the stereochemical properties of the *N*-acylated pyrrole derivatives including indoles and carbazoles. We also hope that the perfect gear system might shed light on the practical use of molecular gears.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For representative review articles on axial chirality, see: (a) Zask, A.; Murphy, J.; Ellestad, G. A. *Chirality* **2013**, *25*, 265−274.

(b) LaPlante, S. R.; Fader, L. D.; Fandrick, K. R.; Fandrick, D. R.; Hucke, O.; Kemper, R.; Miller, S. P. F.; Edwards, P. J. *J. Med. Chem.* **2011**, *54*, 7005−7022. (c) Natsugari, H.; Ikeura, Y.; Kamo, I.; Ishimaru, T.; Ishichi, Y.; Fujishima, A.; Tanaka, T.; Kasahara, F.; Kawada, M.; Doi, T. *J. Med. Chem.* **1999**, *42*, 3982−3993. (d) Lee, S.; Kamide, T.; Tabata, H.; Takahashi, H.; Shiro, M.; Natsugari, H. *Bioorg. Med. Chem.* **2008**, *16*, 9519−9523. (e) Tabata, H.; Akiba, K.; Lee, S.; Takahashi, H.; Natsugari, H. *Org. Lett.* **2008**, *10*, 4871−4874. (f) Tabata, H.; Nakagomi, J.; Morizono, D.; Oshitari, T.; Takahashi, H.; Natsugari, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 3075−3079. (g) Tabata, H.; Wada, N.; Takada, Y.; Oshitari, T.; Takahashi, H.; Natsugari, H. *J. Org. Chem.* **2011**, *76*, 5123−5131. (h) Tabata, H.; Wada, N.; Takada, Y.; Nakagomi, J.; Miike, T.; Shirahase, H.; Oshitari, T.; Takahashi, H.; Natsugari, H. *Chem.—Eur. J.* **2012**, *18*, 1572−1576. (i) Tabata, H.; Yoneda, T.; Oshitari, T.; Takahashi, H.; Natsugari, H. *J. Org. Chem.* **2013**, *78*, 6264−6270.

(2) (a) Takahashi, H.; Wakamatsu, S.; Tabata, H.; Oshitari, T.; Harada, A.; Inoue, K.; Natsugari, H. *Org. Lett.* **2011**, *13*, 760−763. (b) Wakamatsu, S.; Takahashi, Y.; Oshitari, T.; Tani, N.; Azumaya, I.; Katsumoto, Y.; Tanaka, T.; Hosoi, S.; Natsugari, H.; Takahashi, H. *Chem.—Eur. J.* **2013**, *19*, 7056−7063.

(3) Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303−4427.

(4) See Supporting Information for the detailed synthesis of compounds **2**−**5** and the synthesis of the 2′,6′-disubstituted benzoic acids shown in Scheme 1.

(5) For measurements of the $\Delta G^{\ddagger}$ values, see: Petit, M.; Lapierre, A. J. B.; Curran, D. P. *J. Am. Chem. Soc.* **2005**, *127*, 14994−14995.

(6) Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529−2591.

(7) CCDC 977540 (**5I-B**) and 977541 (**5II-B**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

(8) See Supporting Information for conversion between **5II-B** and **5I-A**, and **5I-B** and **5II-A**.

(9) For tertiary aromatic amide systems, see: (a) Clayden, J.; Pink, J. H. *Angew. Chem., Int. Ed.* **1998**, *37*, 1937−1939. (b) Albert, J. S.; Ohnmacht, C.; Bernstein, P. R.; Rumsey, W. L.; Aharony, D.; Alelyunas, Y.; Russell, D. J.; Potts, W.; Sherwood, S. A.; Shen, L.; Dedinas, R. F.; Palmer, W. E.; Russell, K. *J. Med. Chem.* **2004**, *47*, 519−529. (c) Albert, J. S.; Ohnmacht, C.; Bernstein, P. R.; Rumsey, W. L.; Aharony, D.; Masek, B. B.; Dembofsky, B. T.; Koether, G. M.; Potts, W.; Evenden, J. L. *Tetrahedron* **2004**, *60*, 4337−4347. (d) Guile, S. D.; Bantick, J. R.; Cooper, M. E.; Donald, D. K.; Eyssade, C.; Ingall, A. H.; Lewis, R. J.; Martin, B. P.; Mohammed, R. T.; Potter, T. J.; Reynolds, R. H.; St-Gallay, S. A.; Wright, A. D. *J. Med. Chem.* **2007**, *50*, 254−263. (e) Bragg, R. A.; Clayden, J.; Morris, G. A.; Pink, J. H. *Chem.—Eur. J.* **2002**, *8*, 1279−1289. (f) Bragg, R. A.; Clayden, J. *Org. Lett.* **2000**, *2*, 3351−3354. For representative reports including review articles on the molecular gear, see: (g) Iwamura, H.; Mislow, K. *Acc. Chem. Res.* **1988**, *21*, 175−182. (h) Stevens, A. M.; Richards, C. J. *Tetrahedron Lett.* **1997**, *38*, 7805−7808. (i) Setaka, W.; Nirengi, T.; Kabuto, C.; Kira, M. *J. Am. Chem. Soc.* **2008**, *130*, 15762−15763. (j) Kao, C.-Y.; Hsu, Y.-T.; Lu, H.-F.; Ito, C.; Huang, S.-L.; Lin, Y.-C.; Sun, W.-T.; Yang, J.-S. *J. Org. Chem.* **2011**, *76*, 5782−5792.

(10) See Supporting Information for the conversion between **5II-B** and **5I-A** at 100 °C.

(11) Betson, M. S.; Clayden, J.; Worrall, C. P.; Peace, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 5803−5807.

(12) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A. *Gaussian 03*, revision D.02; Gaussian, Inc.: Wallingford, CT, 2004.

(13) See Supporting Information for the detailed calculation method.