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Ring Inversion Dynamics of Derivatives of Thianthrene Di- and Tetraoxide[§]

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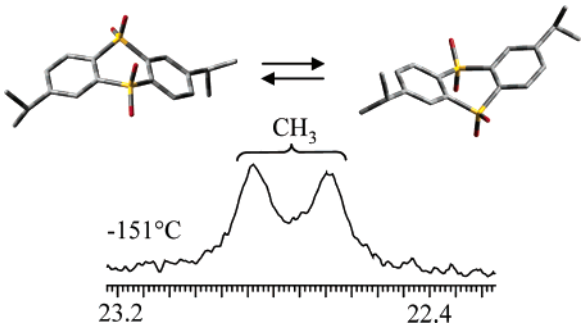


The ring inversion barrier for thianthrene tetraoxide was determined by making use of the variable temperature ^{13}C NMR spectra of the 2,7-diisopropyl derivative ($\Delta G^{\ddagger} = 6.5$ kcal mol^{-1}). The barrier is lower than that measured for a *trans* thianthrene dioxide derivative ($\Delta G^{\ddagger} = 9.35$ kcal mol^{-1}). These results agree well with ab initio theoretical predictions.

Thianthrene and its oxides adopt a flexible boat-type conformation[1] that inverts rapidly at ambient temperature. Thianthrene-5,10-dioxide exists as a *cis* and a *trans* isomer: when the ring inversion of the *trans* isomer is frozen, the static symmetry becomes different from the dynamic symmetry, thus rendering the carbon and hydrogen atoms diastereotopic. This makes anisochronous the corresponding NMR signals and allows the barrier for the ring inversion process to be determined. By making use of an approximate relationship at the coalescence temperature, González-Núñez et al. estimated[2] this barrier to be 10.2 kcal mol^{-1}.

When the more accurate total line shape analysis is applied to the temperature-dependent ^{13}C spectra (Figure 1) of the analogous *trans*-2,7-dimethylthianthrene-5,10-dioxide (**1a**, see Chart 1), a somewhat lower barrier is obtained ($\Delta G^{\ddagger} = 9.35 \pm 0.15$ kcal mol^{-1}). This value agrees with the theoretical (at the B3LYP/6-31G(d) level[3]) prediction for the unsubstituted thianthrene (10.5 kcal mol^{-1}) as well as with the value we obtained, at the same level of theory, for the *trans*-**1a** (10.2 kcal mol^{-1}). This small difference (0.3 kcal mol^{-1}) between the two computed values suggests that the methyl substituents do not affect, in practice, the ring inversion barrier.

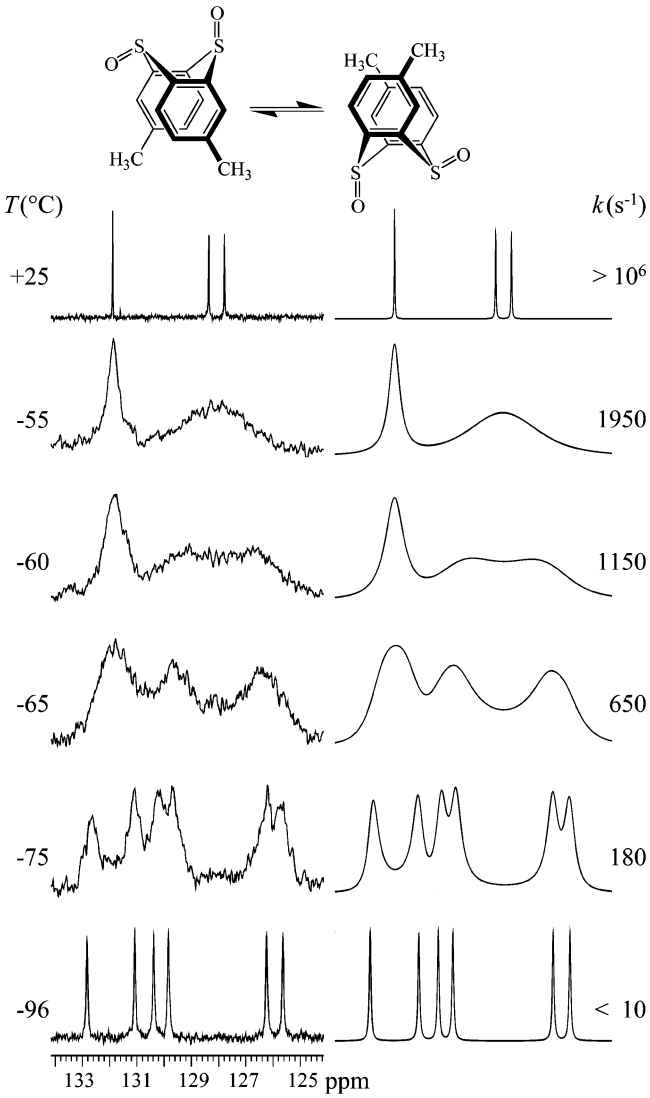
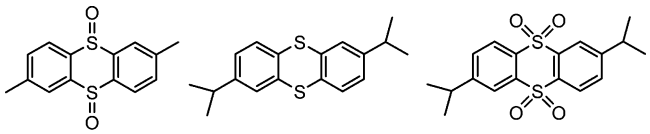


FIGURE 1. Left: temperature dependence of the three ^{13}C aromatic CH signals of **1a** at 150.8 MHz in CD_2Cl_2. Right: line shape simulation obtained with the rate constants indicated.

CHART 1



1a (*trans*)
1b (*cis*)

2

3

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(1) (a) Purcell, K. F.; Berschied, J. R., Jr. *J. Am. Chem. Soc*. **1967**, *89*, 1579−1582. (b) Chickos, J.; Mislow, K. *J. Am. Chem. Soc*. **1967**, *89*, 4815−4816. (c) Bonchio, M.; Conte, V.; De Conciliis, M. A.; Di Furia, F.; Ballistreri, F. P.; Tomaselli, G. A.; Toscano, R. M. *J. Org. Chem*. **1995**, *60*, 4475−4480.

(2) González-Núñez, M. E.; Mello, R.; Royo, J.; Asensio, G.; Monzó, I.; Tomás, F.; García López, J.; López Ortiz, F. *J. Org. Chem*. **2005**, *70*, 3450−3457.

(3) Deubel, D. *J. Org. Chem*. **2001**, *66*, 2686−2691.

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Contrary to the *trans*, the *cis* isomer of thianthrene-5,10-dioxide gives rise to two conformers of different stability.[3] Owing to their C_{2v} symmetry, however, neither of these conformers displays anisochronous NMR signals in the static conformation, so that the barrier can be measured by NMR only if both forms are appreciably populated. This, however, was found not to be the case since line broadening effects, due to an exchange process, were not observed in the ^{1}H NMR spectrum, down to −130 °C.[2] Even when lower temperatures (−170° C) could be reached, the ^{13}C signals of the *cis*-2,7-dimethylthianthrene-5,10-dioxide (**1b**, Chart 1) did not display such an effect.

According to theory,[3] only one of the two conformers is appreciably populated in the *cis* isomer, that is, the one having the two oxygen atoms in a pseudoequatorial position (*endo-endo* SOSO). The corresponding computed energy is, in fact, much lower (11.9−13.6 kcal mol^{-1}) than that of the pseudoaxial conformer (*exo-exo* SOSO). This occurrence explains why it is impossible to observe the exchange process in the NMR spectra and, consequently, to determine the experimental barrier by this method.

Also, thianthrene and thianthrene tetraoxide have symmetries that do not allow one to observe modifications of the equivalence (isochronicity) of the lines of the carbon or hydrogen atoms in the static with respect to the dynamic situation. As a consequence, it is necessary to introduce appropriate substituents to be used as NMR probes for detecting the ring inversion process. For this reason, the 2,7-diisopropyl derivatives (**2** and **3** in Chart 1) were prepared.[4] The two methyl groups within the isopropyl moieties are, in fact, enantiotopic in the presence of fast ring inversion but become diastereotopic, yielding anisochronous (thus NMR distinguishable) signals when this process is frozen.[5]

Unfortunately, the ^{13}C signal of the isopropyl methyl groups of **2** broadens but remains a single line even at −170 °C, suggesting that the barrier is probably lower than 6 kcal mol^{-1}. This is in line with the computations that predict a barrier for thianthrene as low as 5.5 kcal mol^{-1}.[3] We checked again that the presence of the two isopropyl substituents does not affect the interconversion barrier with respect to thianthrene; in fact, according to our ab initio calculations at the same level of theory, the barrier for compound **2** is almost identical (5.4 kcal mol^{-1}). Even lower values can be determined, in principle, by dynamic NMR if the chemical shift differences are sufficiently large.[6] Evidently, in the case of **2**, the ^{13}C shift separation of the methyl signals is smaller (even at 150.8 MHz) than the line width, which is heavily broadened by the viscosity at such low temperatures.

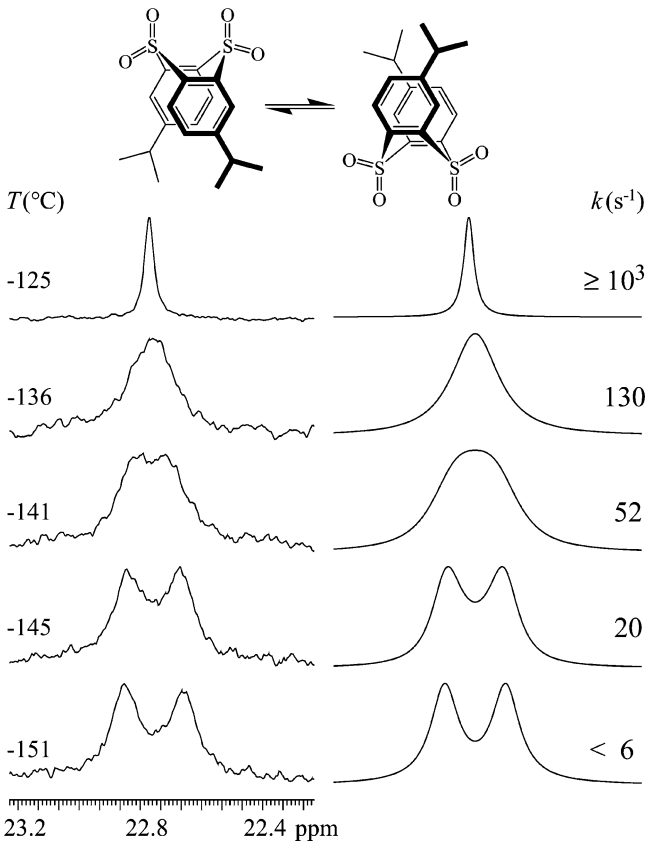

FIGURE 2. Left: temperature dependence of the ^{13}C methyl signal of **3** at 150.8 MHz in $CHF_2Cl/CHFCl_2$. Right: line shape simulation obtained with the rate constants indicated.

Contrary to thianthrene,[7] compound **2** is chiral when the ring inversion is frozen, as it occurs in the solid state. Indeed compound **2** was found to crystallize as a conglomerate, and due to the presence of the heavy sulfur atoms, X-ray diffraction allowed us to identify the absolute structure of one enantiomer within the homochiral crystal by means of the Bijovet method [8] (see Supporting Information).

More promising for an experimental determination of the ring inversion process is the theoretical prediction that the barrier of thianthrene tetraoxide should be larger (i.e., 6.3 kcal mol^{-1})[3] than that of thianthrene: our calculations indicated that essentially the same barrier (6.1 kcal mol^{-1}) is predicted also for the isopropyl substituted derivative **3**.

As reported in Figure 2, the ^{13}C methyl signal of **3** broadens on cooling and eventually splits into two equally intense lines at −151 °C. The rate constants obtained from line shape simulation yield a barrier ($\Delta G^{\ddagger} = 6.5 \pm 0.15$ kcal mol^{-1}) which is in excellent agreement with the value derived by calculations.

These results thus offer an experimental verification of the theory predicting that the ring inversion barrier of thianthrene tetraoxide is significantly smaller than that of the thianthrene dioxide (*trans*).

Experimental Section

4-Isopropylbenzenesulfonyl chloride.[9] The chlorosulfonation of isopropylbenzene was achieved by the procedure of Shirley and

(4) Such types of probes are useless in the case of the *cis*-thianthrene-5,10 dioxide since the presence of the prochiral sulfoxide moiety makes the methyl groups of the isopropyl substituent diastereotopic already at ambient temperature, independently of the fast or slow rate of the ring inversion process.[5]

(5) (a) Mislow, K.; Raban, M. *Top. Stereochem.* **1967**, *1*, 1−38. (b) Jennings, W. B. *Chem. Rev.* **1975**, *75*, 307−322. (c) Eliel, E. L. *J. Chem. Educ.* **1980**, *57*, 52−55. (d) Scott, L. Y.; Hashemi, M. M.; Bratcher, M. S. *J. Am. Chem. Soc.* **1992**, *114*, 1920−1921.

(6) For instance, a $\Delta G^{\ddagger}$ equal to 4.25 kcal mol^{-1} was measured in: (a) Grilli, S.; Lunazzi, L.; Mazzanti, A. *J. Org. Chem.* **2001**, *66*, 4444−4446, and a $\Delta G^{\ddagger}$ equal to 4.5 or 4.6 kcal mol^{-1} was in: (b) Anderson, J. E.; de Meijere, A.; Kozhushkov, S. I.; Lunazzi, L.; Mazzanti, S. *J. Am. Chem. Soc.* **2001**, *124*, 6706−6713. (c) Lunazzi, L.; Mazzanti, A.; Minzoni, M. *J. Org. Chem.* **2005**, *70*, 456−462.

(7) Larson, S. B.; Simonsen, S. H.; Martin, G. E.; Smith, K.; Puig-Torres, S. *Acta Crystallogr. Sect. C* **1984**, *40*, 103−106.

(8) Bijvoet, J. M.; Peerdeman, A. F.; van Bommel, A. I. *Nature* **1951**, *168*, 271−272.

Letho.[10] To a solution of isopropyl benzene kept at 0 °C (35 mL, 0.25 mol in 75 mL of $CHCl_3$) was slowly dropped the chlorosulfonic acid (50 mL, 0.75 mol), keeping the temperature at 0 °C. The mixture was stirred overnight at room temperature, then was poured on crushed ice and extracted with $CHCl_3$, and the collected organic phase was dried on $MgSO_4$ and concentrated at reduced pressure. The crude product was distilled to yield 28 mL (62%) of pure colorless liquid, bp_5 131 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ 1.28 (d, 6H, J = 7.0 Hz), 3.02 (septet, 1H, J = 7.0 Hz), 7.42 (m, 2H), 7.94 (m, 2H). ^{13}C NMR ($CDCl_3$, 75.4 MHz, 25 °C): δ 23.8 (2 Me), 34.5 (CH), 127.4 (2CH), 127.9 (2CH), 142.1 (quat), 157.6 (quat).

4-Isopropylbenzenethiol.[9] To a suspension of $LiAlH_4$ (12.0 g, 0.316 mol) in 50 mL of dry Et_2O cooled to 0 °C was dropped, in 30 min, a solution of 4-isopropylbenzenesulfonyl chloride (20.0 g, 92 mmol, in 100 mL of Et_2O). After refluxing for 3 h, the reaction was complete. The mixture was again cooled to 5 °C, and the exceeding hydride was destroyed by dropping carefully a saturated aqueous solution of NH_4Cl. The rough mass was filtered and the organic phase separated, dried on $MgSO_4$, and concentrated at reduced pressure to yield 8.1 g (58%) of product that was directly used in the next step. ^{1}H NMR ($CDCl_3$, 300 MHz, 25 °C): δ 1.11 (d, 6H, J = 7.1 Hz), 2.82 (septet, 1H, J = 7.1 Hz), 3.39 (s, 1H), 7.09 (m, 2H), 7.21 (m, 2H). ^{13}C NMR ($CDCl_3$, 75.4 MHz, 25 °C): δ 24.0 (2Me), 33.7 (CH), 127.0 (quat), 127.3 (2CH), 129.9 (2CH), 146.5 (quat).

2,7-Diisopropylthianthrene (2). A mixture of 4-isopropylbenzenethiol (2.0 g, 13.1 mmol) and 8 mL of 98% H_2SO_4 was stirred overnight at room temperature, then cooled with ice, carefully neutralized with a solution of KOH, and extracted with Et_2O. The organic layers were collected and dried on $MgSO_4$. The purification of the crude product by chromatography, on a silica gel column eluted with hexane/ethyl acetate 95/5, yielded 500 mg (25%) of **2** as a white solid that was further purified by semipreparative HPLC (Waters NovaPack, 5 μm silica, 300 × 19 mm, 24 mL/min, *n*-hexane/2-propanol 99/1). ^{1}H NMR ($CDCl_3$, 600 MHz, 25 °C): δ 1.21 (d, 6H, J = 7.0 Hz), 2.85 (septet, 1H, J = 7.0 Hz), 7.10 (dd, 2H, J = 2.1, 8.2 Hz), 7.36 (d, 2H, J = 2.1 Hz), 7.41(d, 2H, J = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 150.8 MHz, 25 °C): δ 23.9 (2Me), 33.8 (CH), 126.0 (CH), 126.8 (CH), 128.6 (CH), 132.6 (quat), 135.9 (quat), 148.9 (quat). Anal. Calcd for $C_{18}H_{20}S_2$: C, 71.95; H, 6.71; S, 21.34. Found: C, 71.84; H, 6.67; S, 21.29.

2,7-Dimethylthianthrene[11] was prepared from *p*-thiocresol with the same procedure described for **2**. ^{1}H NMR ($CDCl_3$, 600 MHz, 25 °C): δ 2.28 (s, 3H), 6.99 (dd, 1H, J = 1.6, 7.9 Hz), 7.26 (d, 1H, J = 1.6 Hz), 7.31 (d, 1H, J = 7.9 Hz). ^{13}C NMR ($CDCl_3$, 150.8 MHz, 25 °C): δ 20.9 (2Me), 128.4 (CH), 128.5 (CH), 129.3 (CH), 132.2 (quat), 135.9 (quat), 137.7 (quat).

2,7-Dimethylthianthrene-5,10-dioxide-*trans* (1a) and -*cis* (1b)[12] were prepared by oxidation of the 2,7-dimethylthianthrene with hydrogen peroxide in acidic media.[1c] **1a:** ^{1}H NMR ($CDCl_3$, 600 MHz, 25 °C) δ 2.47 (s, 3H), 7.46 (dd, 1H, dd, 1H, J = 1.7, 7.8 Hz), 7.89 (d, 1H, J = 1.7 Hz), 7.95 (d, 1H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 150.8 MHz, 25 °C) δ 21.75 (2Me), 127.71 (CH), 128.25 (CH), 131.72 CH), 139.46 (quat), 142.52 (quat), 142.95 (quat). **1b:** ^{1}H NMR ($CDCl_3$, 600 MHz, 25 °C) δ 2.50 (s, 3H), 7.52 (d, 1H, J = 7.8 Hz), 7.82 (d, 1H, J = 1.5 Hz), 7.87 (dd, 1H, J = 7.8, 1.5 Hz); ^{13}C NMR ($CDCl_3$, 150.8 MHz, 25 °C) δ 21.7 (2Me), 123.5 (CH), 123.9 (CH), 131.4 (CH), 134.4 (quat), 137.7 (quat), 141.8 (quat).

2,7-Diisopropylthianthrene-5,5,10,10-tetraoxide (3) was prepared by oxidation of **2** with *m*-chloroperbenzoic acid.[1c] ^{1}H NMR ($CDCl_3$, 600 MHz, 25 °C): δ 1.31 (d, 6H, J = 6.9 Hz), 3.09 (septet, 1H, J = 6.9 Hz), 7.64 (dd, 2H, J = 1.7, 8.0 Hz), 8.09 (d, 2H, J = 1.7 Hz), 8.17 (d, 2H, J = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 150.8 MHz, 25 °C): δ 23.6 (2Me), 34.8 (CH), 124.2 (CH), 126.5 (CH), 131.7 (CH), 137.1 (quat), 140.0 (quat), 156.2 (quat). Anal. Calcd for $C_{18}H_{20}S_2O_4$: C, 59.32; H, 5.53; S, 17.59. Found: C, 59.15; H, 5.50; S, 17.45.

NMR Measurements. NMR spectra were recorded at 600 MHz for ^{1}H and 150.8 MHz for ^{13}C. The assignments were obtained by DEPT and two-dimensional experiments (g-HSQC and g-HMBC). The samples for the ^{13}C NMR low-temperature measurements were prepared by connecting to a vacuum line the NMR tubes containing the compound and some C_6D_6 for locking purpose and condensing therein the gaseous CHF_2Cl and $CHFCl_2$ under cooling with liquid nitrogen. The tubes were subsequently sealed in vacuo and introduced into the precooled probe of the spectrometer. The temperatures were calibrated by substituting the sample with a precision Cu/Ni thermocouple before the measurements. A complete fitting of NMR line shapes was carried out using a PC version of the DNMR-6 program.[13]

Computational Details. Ab initio computations of **1a**, **2**, and **3** were carried out at the B3LYP/6-31G(d) level by means of the Gaussian 03 series of programs[14] (the standard Berny algorithm in redundant internal coordinates and default criteria of convergence were employed). Harmonic vibrational frequencies were calculated in order to ascertain the nature of the stationary points. For the optimized ground states, the frequency analysis showed the absence of imaginary frequencies, whereas for each transition state, the frequency analysis showed a single imaginary frequency. The corresponding optimized structures are reported in the Supporting Information.

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Supporting Information Available: X-ray structure of compound **2** and ab initio computational data for compounds **1a**, **2**, and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Giovani, E.; Napoletano, E. *Gazz. Chim. Ital*. **1993**, *123*, 257−260.
(10) Shirley, D. A.; Letho, E. A. *J. Am. Chem. Soc*. **1957**, *79*, 3481−3485.
(11) (a) Carey, A. A.; Schram, E. P. *Inorg. Chem. Acta* **1982**, *59*, 75−78 and 79−91. (b) Giordan, J.; Bock, H. *Chem. Ber*. **1982**, *115*, 2548−2549.
(12) Mislow, K.; Schneider, P.; Ternay, A. L., Jr. *J. Am. Chem. Soc*. **1964**, *86*, 2957−2958.
(13) *QCPE program No. 633*, Indiana University, Bloomington, IN.
(14) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; 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.; Pople, J. A. *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.