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VIP Chiral Macrocycles

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An Enantiomerically Pure Alleno-Acetylenic Macrocycle: Synthesis and Rationalization of Its Outstanding Chiroptical Response

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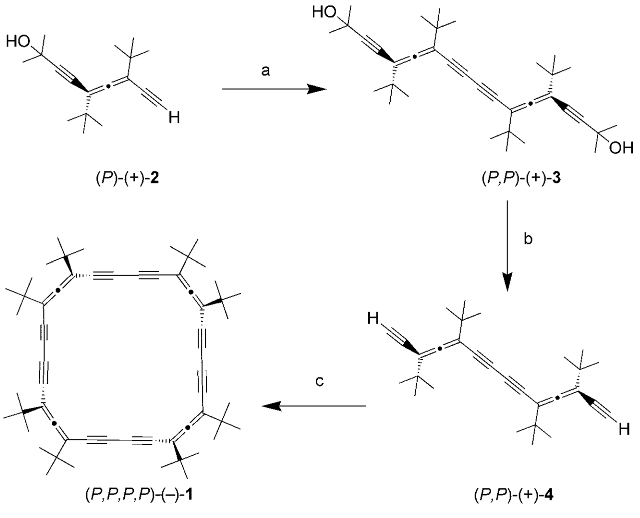
Dedicated to Prof. Dr. Roeland J. M. Nolte on the occasion of his 65th birthday

Chiral allenes attract increasing interest owing to the development of improved syntheses and their emerging use in pharmaceuticals.[1] While strained small-ring allenes have been investigated in greater detail for their theoretical properties and their limits of stability and isolability,[2] allenic macrocycles, in particular shape-persistent ones,[3] are mostly unknown.[4] The scarcity of allenic macrocycles is rather surprising in view of the opportunities for creating new nonplanar, chiral topologies and for developing new chiral host molecules. The first allenic macrocycle known was a [3_4]cyclophane, reported by Krause and co-workers,[5] in which four *p*-phenylene moieties are bridged by four 1,3-dimethylallene-1,3-diyl linkers and which was isolated as a mixture of several stereoisomers. Fallis and co-workers reported the preparation of the first optically active allenophanes.[6] Despite their elegant methodologies , clear proof of the enantiomeric purity of the final compounds was not provided. Furthermore, the absolute configuration of the allene moieties was not unambiguously determined, but only inferred from the reaction mechanism.

In our group, we have shown that di-*tert*-butyl-diethynylallenes (DEAs) are stable chiral building blocks.[7] Racemic mixtures of DEAs were converted into stereoisomeric mixtures of an alleno-acetylenic macrocycle and an allenophane. All diastereoisomers were separated and characterized,[8] but the enantiomers were not resolved. In this sense, much information concerning the structural, chiroptical, and electronic properties of chiral allenic macrocycles is still missing.

A deeper understanding of a chiroptical response, obtained from electronic circular dichroism (CD) spectroscopy,[9] can be accomplished by full CD calculations using quantum-mechanical methods. Such calculations provide more complex information regarding the assignment of Cotton effects to specific transitions, determination of absolute configuration, and even investigation of conformational preferences.[10] Nevertheless, to relate the chiroptical properties to structural and electronic features, conformationally stable compounds are desirable.

Macrocyclization of a DEA building block by acetylenic homocoupling, following the three-step protocol shown in Scheme 1, is expected to yield the alleno-acetylenic tetramer macrocycle **1**. When the racemic DEA derivative (±)-**2** is used, the cyclization affords six stereoisomers of macrocycle **1**, including two racemates and two achiral diastereoisomers. The two racemates are the D_4-symmetric (all the *tert*-butyl groups are magnetically equivalent) (*M*,*M*,*M*,*M*)/(*P*,*P*,*P*,*P*)-**1** pair with crown geometry and the C_2-symmetric (four magnetically different *tert*-butyl groups) (*M*,*M*,*M*,*P*)/(*P*,*P*,*P*,*M*)-**1** pair with twist geometry. The two achiral isomers are C_{2h}-symmetric (two magnetically different *tert*-butyl groups) (*P*,*P*,*M*,*M*)-**1** with chair geometry and D_{2d}-symmetric



Scheme 1. Enantioselective synthesis of the macrocycle (*P*,*P*,*P*,*P*)-(−)-**1**. Reagents and conditions: a) [$PdCl_2(PPh_3)_2$], CuI, TMEDA, toluene, 50°C, 24 h, 99%, d.r. (*P*,*P*)-**3**/(*P*,*M*)-**3**/(*M*,*M*)-**3** 100:0:0; b) NaOH, toluene, 90°C, 10 h, 65%, d.r. (*P*,*P*)-**4**/(*P*,*M*)-**4**/(*M*,*M*)-**4** 100:0:0; c) CuCl, $CuCl_2$, pyridine, RT, then addition of (*P*,*P*)-**4** over 20 h, 68%, d.r. (*P*,*P*,*P*,*P*)-**1**/(*M*,*P*,*P*,*P*)-**1**)/(*P*,*P*,*M*,*M*)-**1**/(*P*,*M*,*P*,*M*)-**1**/(*M*,*M*,*M*,*P*)-**1**/(*M*,*M*,*M*,*M*)-**1** 100:0:0:0:0:0. TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

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(all the *tert*-butyl groups are magnetically equivalent) (*P*,*M*,*P*,*M*)-**1** with boat geometry (Figure 1). The targeted crown macrocycle (*M*,*M*,*M*,*M*)/(*P*,*P*,*P*,*P*)-**1** is expected to be conformationally highly stable and shape-persistent. The conformational analysis of this system was carried out at the AM1 level of theory by systematic variation of the dihedral angle between opposite sides of the macrocycle. All the initial structures converged to the same minimum. The minimum found was further optimized at the B3LYP/6-31G(d) level of theory (the Cartesian coordinates can be found in the Supporting Information).

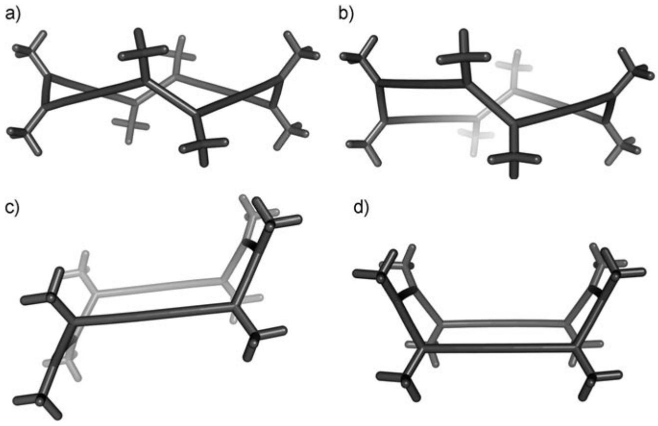

Figure 1. Isomers of **1**. a) (*P*,*P*,*P*,*P*)-**1** (crown), b) (*P*,*P*,*P*,*M*)-**1** (twist), c) (*P*,*P*,*M*,*M*)-**1** (chair), and d) (*M*,*P*,*M*,*P*)-**1** (boat). The conformations were optimized at the AM1 level of theory.

The enantiopure macrocycles (*P*,*P*,*P*,*P*)-(−)-**1** and (*M*,*M*,*M*,*M*)-(+)-**1** were obtained starting from optically pure DEA derivatives (*P*)-(+)-**2** and (*M*)-(-)-**2**, respectively (Scheme 1). Recently, we reported the synthesis of nearly enantiopure (*P*)-(+)-**2** and (*M*)-(−)-**2** in 69 % yield with an enantiomer ratio (e.r.) of 96:4.[11] X-ray crystallographic analysis confirmed the first example for a palladium-mediated enantioselective *syn*-S_N2'-type cross-coupling reaction of an alkyne with an optically pure bispropargylic ester. Subsequently, the DEA derivatives (*M*)-(−)-**2** and (*P*)-(+)-**2** were obtained in enantiopure form after resolution by HPLC methods on a chiral stationary phase.

The enantiomerically pure DEA derivative (*P*)-(+)-**2** was dimerized by palladium-catalyzed oxidative homocoupling[12] to yield (*P*,*P*)-(+)-**3** quantitatively. After deprotection, macrocycle (*P*,*P*,*P*,*P*)-(−)-**1** was obtained in a one-pot dimerization–cyclization reaction of compound (*P*,*P*)-(+)-**4** under Eglinton–Galbraith conditions. To favor the cyclization over oligomerization, a solution of (*P*,*P*)-(+)-**4** in pyridine was added slowly to the solution of $CuCl/CuCl_2$ in pyridine over a period of 20 h. Under these conditions (*P*,*P*,*P*,*P*)-(−)-**1** was obtained in a yield of 68 %. Similarly, the (*M*,*M*,*M*,*M*)-(+)-**1** enantiomer was obtained starting from enantiomerically pure (*M*)-(−)-**2** (a detailed description of the synthesis and the NMR spectra are shown in the Supporting Information).

The proposed structure of the new enantiomeric macrocycles was fully confirmed by the spectral data. In the MALDI MS, the protonated molecular ion $[M+H]^+$ appeared as the parent ion at *m*/*z* 793. The D_4 symmetry of the macrocycles was supported by the NMR spectra (in $CDCl_3$; see the Supporting Information). The ^{1}H NMR spectrum displayed a single resonance for the 72 *tert*-butyl protons at $\delta = 1.16$ ppm, whereas the ^{13}C NMR spectrum featured two *tert*-butyl resonances at $\delta = 29.0$ and 35.8 ppm. In addition, one peak was observed at $\delta = 216.2$ ppm for the central carbon atom in the allene moieties. The stability of compounds (*P*,*P*,*P*,*P*)-(−)-**1** and (*M*,*M*,*M*,*M*)-(+)-**1** (m.p. 220 °C (decomp.)) is remarkable. The macrocycles show no decomposition or isomerization/racemization upon heating in solution to 110 °C, as ascertained by both ^{1}H NMR and CD spectroscopy. They are also stable under air atmosphere and in the presence of moisture for weeks. Unlike other allenic π chromophores previously reported,[8,11] these macrocycles do not undergo photoisomerization under daylight. The CD curves for both enantiomers are mirror images along the abscissa (Figure 2). The CD spectra show extremely intense Cotton effects, with an intensity of the peaks around 253 nm of $\Delta\varepsilon = \pm 790\,\mathrm{M^{-1}\,cm^{-1}}$. There are literature reports of chiral macrocyclic,[13a,b] polycyclic,[13c,d] and acyclic[13e–i] compounds that show strong CD intensities. In most of these cases, the intense CD bands can be represented by a sum of contributions of the monomeric units. In contrast, the $\Delta\varepsilon_{max}$ intensities of (*P*,*P*,*P*,*P*)-(−)-**1** and (*M*,*M*,*M*,*M*)-(+)-**1** are approximately 100 times greater than those of the corresponding monomers (*P*)-(+)-**2** and (*M*)-(−)-**2** and roughly eight times greater than those of the dimers (*P*,*P*)-(+)-**4** and (*M*,*M*)-(−)-**4** (see the Supporting Information).

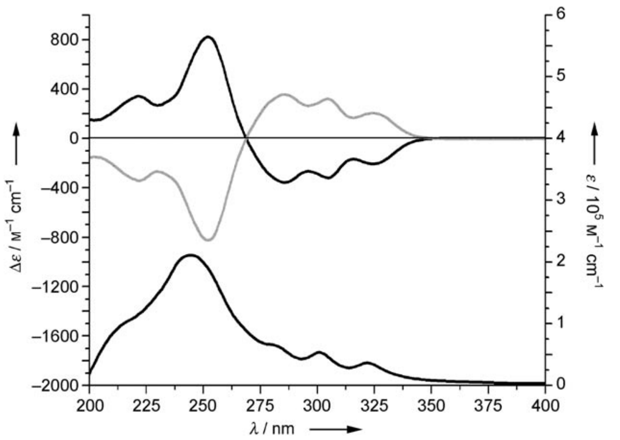

Figure 2. Top: CD spectra of enantiopure (*P*,*P*,*P*,*P*)-(−)-**1** (black line) and enantiopure (*M*,*M*,*M*,*M*)-(+)-**1** (gray line), measured in *n*-hexane. Bottom: UV/Vis spectrum measured in *n*-hexane.

To determine the origin of such outstanding chiroptical properties, the *g*-factor plot was analyzed (Figure 3). The *g*-factor is defined as the ratio between the molar circular dichroism Δε and the molar extinction coefficient ε ($g = \Delta\varepsilon/\varepsilon$).[14] The *g*-factor plot can be used to estimate the relative contributions of electric and magnetic transition dipole moments to the Cotton effects. In the case of (*P*,*P*,*P*,*P*)-(−)-**1**, the larger *g*-values between 350 nm and 270 nm clearly

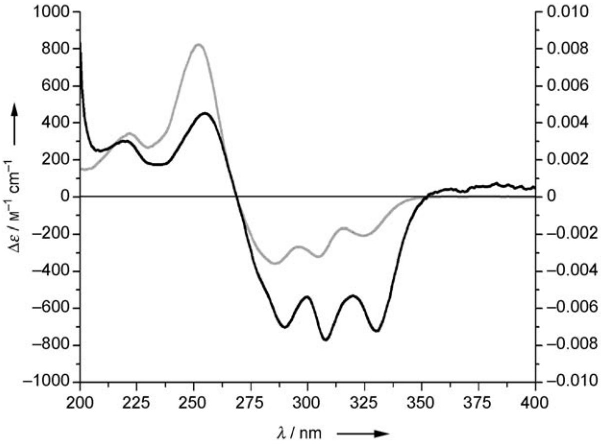

Figure 3. CD spectrum (gray line) and *g*-factor plot (black line) for (*P*,*P*,*P*,*P*)-(−)-**1**. UV/Vis and CD spectra were measured in *n*-hexane.

indicate stronger magnetic dipole contributions, while the opposite is evident with regard to the Cotton effects around 253 nm.

To prove the absolute configuration of macrocycle (*P*,*P*,*P*,*P*)-(−)-**1** and to gain further insight into the origin of the Cotton effects, quantum-mechanical calculations of the CD spectrum were performed using the semiempirical method ZINDO.[15] The basic pattern of the CD curve including the sign, magnitude, and position of Cotton effects, but not the vibronic structures[16] around 350–270 nm (see the Supporting Information), was reproduced well by the ZINDO calculation.[17] Therefore, the absolute configuration of macrocycle (−)-**1** was determined as *P*,*P*,*P*,*P* also by the theoretical calculation.

The calculated Cotton effect at 296 nm is produced mainly by the transition S1 (Figure 4). The calculated rotational strength (*R*) of this transition is remarkably high. *R* is obtained as the scalar product of the electric transition dipole moment (ETDM) and the magnetic transition dipole moment (MTDM). The analysis of S1 reveals that the value of *R* is dominated by the MTDM contribution (see the ETDMs and MTDMs of selected transitions in the Supporting Information). Both transition dipole moments of S1 are perpendicular to the ring plane, as depicted in Figure 5, where two vectors are antiparallel to each other (angle between the two vectors: $\theta = 180°$) and hence the rotational strength is negative. Since the MTDM of S1 is much larger than its ETDM, the rotational strength of S1 is mostly governed by its MTDM, in agreement with the experimentally observed *g*-factor (configuration interaction coefficients of the MOs for the relevant transitions and selected MO plots can be found in the Supporting Information).

The Δε value of the CD band at 252 nm is one of the largest ever reported.[13] This CD band originates from the degenerate transitions S2 and S3 (Figure 4). ETDM and MTDM of S2 are parallel to each other, giving rise to a positive Cotton effect (see the Supporting Information). The ETDM and MTDM of S3 are also parallel to each other, also giving rise to a positive Cotton effect. Further studies on the mechanism of such intense CDs and the fascinating topology of the MOs involved in these transitions are underway.

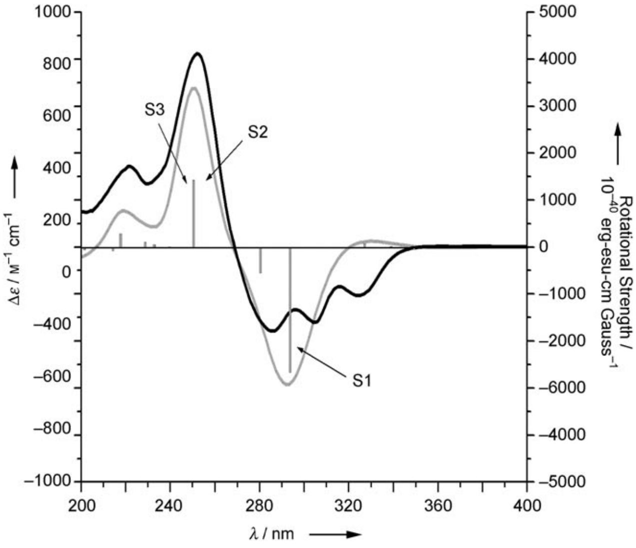

Figure 4. Experimental CD spectrum (black line) measured in *n*-hexane, calculated spectrum (gray line, ZINDO; for more information see the Supporting Information), and rotational strength (gray bars, ZINDO) for (*P*,*P*,*P*,*P*)-(−)-**1**.

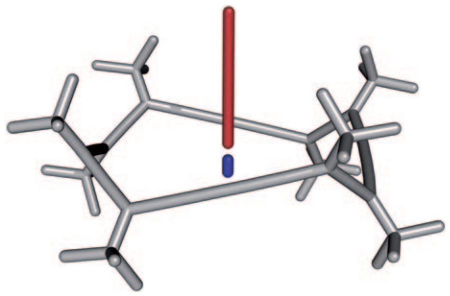

Figure 5. MTDM (red line) and ETDM (blue line) of transition S1 in (*P*,*P*,*P*,*P*)-(−)-**1** (ZINDO).

In summary, the first enantiomerically pure alleno-acetylenic macrocycles were synthesized. The origin of the main CD band proposed by the calculations was found to be in accordance with the experimental conclusion obtained from the *g*-factor plot. The unique combination of geometric and electronic properties explains the magnitude of the Cotton effects. This study suggests that exceptional CD intensities can be expected for helical alleno-acetylenic oligomers and supramolecular assemblies of alleno-acetylenic macrocycles, reaching to unprecedented Δε values.

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[1] a) *Modern Allene Chemistry*, *Vols. 1 and 2* (Eds.: N. Krause, A. S. K. Hashmi), Wiley-VCH, Weinheim, **2004**; b) A. Hoff-

mann-Röder, N. Krause, *Angew. Chem.* **2002**, *114*, 3057–3059; *Angew. Chem. Int. Ed.* **2002**, *41*, 2933–2935; c) A. Hoffmann-Röder, N. Krause, *Angew. Chem.* **2004**, *116*, 1216–1236; *Angew. Chem. Int. Ed.* **2004**, *43*, 1196–1216.

[2] H. Hopf, *Classics in Hydrocarbon Chemistry*, Wiley-VCH, Weinheim, **2000**, pp. 171–196.

[3] a) C. S. Jones, M. J. O'Connor, M. M. Haley in *Acetylene Chemistry: Chemistry, Biology, and Material Science* (Eds.: F. Diederich, P. J. Stang, R. R. Tykwinski), Wiley-VCH, Weinheim, **2005**, pp. 303–385; b) S. Höger in *Acetylene Chemistry: Chemistry, Biology, and Material Science* (Eds.: F. Diederich, P. J. Stang, R. R. Tykwinski), Wiley-VCH, Weinheim, **2005**, pp. 427–452; c) W. Zhang, J. S. Moore, *J. Am. Chem. Soc.* **2004**, *126*, 12796.

[4] a) M. Nakagawa, *Angew. Chem.* **1979**, *91*, 215–226; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 202–214; b) T. Kawase, *Angew. Chem.* **2005**, *117*, 7500–7502; *Angew. Chem. Int. Ed.* **2005**, *44*, 7334–7336.

[5] S. Thorand, F. Vögtle, N. Krause, *Angew. Chem.* **1999**, *111*, 3929–3931; *Angew. Chem. Int. Ed.* **1999**, *38*, 3721–3723.

[6] a) M. D. Clay, A. G. Fallis, *Angew. Chem.* **2005**, *117*, 4107–4110; *Angew. Chem. Int. Ed.* **2005**, *44*, 4039–4042; b) M. Leclère, A. Fallis, *Angew. Chem.* **2008**, *120*, 578–582; *Angew. Chem. Int. Ed.* **2008**, *47*, 568–572.

[7] a) R. C. Livingston, L. R. Cox, V. Gramlich, F. Diederich, *Angew. Chem.* **2001**, *113*, 2396–2399; *Angew. Chem. Int. Ed.* **2001**, *40*, 2334–2337; b) R. Livingston, L. R. Cox, S. Odermatt, F. Diederich, *Helv. Chim. Acta* **2002**, *85*, 3052–3077.

[8] S. Odermatt, J. L. Alonso-Gómez, P. Seiler, M. M. Cid, F. Diederich, *Angew. Chem.* **2005**, *117*, 5203–5207; *Angew. Chem. Int. Ed.* **2005**, *44*, 5074–5078.

[9] a) N. Berova, K. Nakanishi, R. W. Woody, *Circular Dichroism: Principles and Applications*, Wiley-VCH, New York, **2000**; b) N. Harada, K. Nakanishi, *Circular Dichroic Spectroscopy Exciton Coupling in Organic Stereochemistry*, University Science Books, Mill Valley, California, and Oxford University Press, Oxford, **1983**.

[10] J. L. Alonso-Gómez, A. G. Petrovic, N. Harada, P. Rivera-Fuentes, N. Berova, F. Diederich, *Chem. Eur. J.* **2009**, DOI: 10.1002/chem200900103.

[11] J. L. Alonso-Gómez, P. Schanen, P. Rivera-Fuentes, P. Seiler, F. Diederich, *Chem. Eur. J.* **2008**, *14*, 10564–10568.

[12] R. Rossi, A. Carpita, C. Bigelli, *Tetrahedron Lett.* **1985**, *26*, 523–526.

[13] a) H. Langhals, R. Ismael, *Eur. J. Org. Chem.* **1998**, 1915–1917; b) G. Wulff, S. Krieger, B. Kuehneweg, A. Steigel, *J. Am. Chem. Soc.* **1994**, *116*, 409–410; c) R. S. Walters, C. M. Kraml, N. Byrne, D. M. Ho, Q. Qin, F. J. Coughlin, S. Bernhard, R. A. Pascal, Jr., *J. Am. Chem. Soc.* **2008**, *130*, 16435–16441; d) H. Langhals, J. Gold, *Liebigs Ann.* **1997**, 1151–1153; e) G. P. Spada, *Angew. Chem.* **2008**, *120*, 646–648; *Angew. Chem. Int. Ed.* **2008**, *47*, 636–638; f) R. Amemiya, N. Saito, M. Yamaguchi, *J. Org. Chem.* **2008**, *73*, 7137–7144; g) T. Takata, Y. Furusho, K. Murakawa, T. Endo, H. Matsuoka, T. Hirasa, J. Matsuo, M. Sisido, *J. Am. Chem. Soc.* **1998**, *120*, 4530–4531; h) H. Ito, Y. Furusho, T. Hasegawa, E. Yashima, *J. Am. Chem. Soc.* **2008**, *130*, 14008–14015; i) R. Amemiya, M. Yamaguchi, *Chem. Rec.* **2008**, *8*, 116–127.

[14] a) W. Kuhn, *Z. Phys. Chem. Abt. B* **1929**, *4*, 14–36; b) G. Snatzke, *Angew. Chem.* **1979**, *91*, 380–393; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 363–377; c) S. F. Mason, *Molecular Optical Activity & the Chiral Discrimination*, Cambridge University Press, Cambridge, **1982**, pp. 47–50.

[15] M. Zerner in *Reviews in Computational Chemistry, Vol. 2* (Eds.: K. Lipkowitz, D. Boyd), VCH Publishers, New York, **1991**, pp. 313–365, and references therein.

[16] J. Dale in *Chemistry of Acetylenes* (Ed.: H. G. Viehe), Marcel Dekker, New York, **1969**, pp. 58–70.

[17] All calculations were conducted with Gaussian 03: Gaussian 03 (Revision C.02): M. J. Frisch et al., Gaussian, Inc., Wallingford CT, **2004**; see the Supporting Information.