JOC*Article*

Determination of Absolute Configuration Using Density Functional Theory Calculation of Optical Rotation: Chiral Alkanes

D. M. McCann and P. J. Stephens*

Department of Chemistry, University of Southern California, Los Angeles, California 90089-0482

J. R. Cheeseman

Gaussian Inc., 340 Quinnipiac Street, Bldg 40, Wallingford, Connecticut 06492-4050

pstephen@usc.edu

Received August 16, 2004

The recently developed Gauge-Invariant (Including) Atomic Orbital (GIAO) based Time-Dependent Density Functional Theory (TDDFT) methodology for the calculation of transparent spectral region optical rotations of chiral molecules provides a new approach to the determination of absolute configurations. Here, we discuss the application of the TDDFT/GIAO methodology to chiral alkanes. We report B3LYP/aug-cc-pVDZ calculations of the specific rotations of the 22 chiral alkanes, **2**−**23**, of well-established Absolute Configuration. The average absolute deviation of calculated and experimental $[\alpha]_D$ values for molecules **2**−**22** is 24.8. In two of the molecules **2**−**23**, *trans*-pinane, **10**, and *endo*-isocamphane, **13**, the sign of $[\alpha]_D$ is incorrectly predicted. Our results demonstrate that absolute configurations of alkanes can be reliably assigned by using B3LYP/aug-cc-pVDZ TDDFT/GIAO calculations if, but only if, $[\alpha]_D$ is significantly greater than 25. In the case of (−)-*anti-trans-anti-trans-anti-trans*-perhydrotriphenylene, **1**, $[\alpha]_D$ is −93 and TDDFT/GIAO calculations reliably lead to the absolute configuration *R*(−).

Introduction

Over the last fifty years, the Optical Rotatory Dispersion (ORD) and Circular Dichroism (CD) associated with electronic absorption have been widely employed for the determination of the Absolute Configurations (AC's) of chiral molecules.[1] These methods require that the electronic excitations of the molecule of interest lie in the experimentally accessible spectral region for ORD and CD measurement, which is generally the near-UV ($\lambda \gtrsim$ 200 nm). AC's cannot be determined for molecules which are transparent over this region.

Very recently, a dramatic advance has occurred in the theoretical prediction of the optical rotations of chiral molecules in *transparent* spectral regions. Specifically, the technique of Time-Dependent Density Functional Theory (TDDFT) has been applied to the calculation of transparent spectral region optical rotations.[2] To the extent characterized to date, TDDFT optical rotations compare well to experimental rotations when the functional and basis set used are well-chosen.[3] This advance now permits the AC of a chiral molecule to be determined from its optical rotation at any wavelength in the transparent spectral range. This development provides organic chemists with a new approach to determining absolute configurations, and applications of this approach have already been reported.[4] It is particularly attractive in view of the simplicity of the measurement of optical rotation and the widespread availability of polarimeters operating at discrete wavelengths in the visible and near-UV spectral regions.

(1) (a) Djerassi, C. *Optical Rotatory Dispersion*: *Applications to Organic Chemistry*; McGraw-Hill: New York, 1960. (b) Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy*: *Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983. (c) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; Chapter 13. (d) Lightner, D. A.; Gurst, J. E. *Organic Conformational Analysis and Stereochemistry from Circular Dichroism Spectroscopy*; Wiley-VCH: New York, 2000. (e) *Circular Dichroism*: *Principles and Applications*; Berova, N., Nakanishi, K., Woody, R. W., Eds.; Wiley-VCH: New York, 2000.

(2) (a) Cheeseman, J. R.; Frisch, M. J.; Devlin, F. J.; Stephens, P. J. *J. Phys. Chem. A* **2000**, *104*, 1039. (b) Stephens, P. J.; Devlin, F. J.; Cheeseman, J. R.; Frisch, M. J. *J. Phys. Chem. A* **2001**, *105*, 5356. (c) Mennucci, B.; Tomasi, J.; Cammi, R.; Cheeseman, J. R.; Frisch, M. J.; Devlin, F. J.; Gabriel, S.; Stephens, P. J. *J. Phys. Chem. A* **2002**, *106*, 6102. (d) Grimme, S. *Chem. Phys. Lett.* **2001**, *339*, 380. (e) Grimme, S.; Furche, F.; Ahlrichs R. *Chem. Phys. Lett.* **2002**, *361*, 321. (f) Autschbach. J.; Patchkovskii. S.; Ziegler, T.; van Gisbergen, S. J. A.; Baerends, E. J. *J. Chem. Phys.* **2002**, *117*, 581. (g) Ruud, K.; Helgaker, T. *Chem. Phys. Lett.* **2002**, *352*, 533.

(3) (a) Stephens, P. J.; Devlin, F. J.; Cheeseman, J. R.; Frisch, M. J.; Mennucci, B.; Tomasi, J. *Tetrahedron*: *Asymmetry* **2000**, *11*, 2443. (b) Stephens, P. J.; Devlin, F. J.; Cheeseman, J. R.; Frisch, M. J. *Chirality* **2002**, *14*, 288. (c) Grimme, S.; Bahlmann, A.; Haufe, G. *Chirality* **2002**, *14*, 793. (d) Polavarapu, P. L. *Chirality* **2002**, *14*, 768. (e) Polavarapu, P. L.; Petrovic, A.; Wang, F. *Chirality* **2003**, *15*, S143. (f) Müller, T.; Wiberg, K. B.; Vaccaro, P. H.; Cheeseman, J. R.; Frisch, M. J. *J. Opt. Soc. Am. B*: *Opt. Phys.* **2002**, *19*, 125. (g) Wiberg, K. B.; Vaccaro, P. H.; Cheeseman, J. R. *J. Am. Chem. Soc.* **2003**, *125*, 1888. (h) Wang, F.; Polavarapu, P. L.; Drabowicz, J.; Kielbasinski, P.; Potrzebowski, M. J.; Mikolajczyk, M.; Wieczorek, M. W.; Majzner, W. W.; Lazewska, I. *J. Phys. Chem. A* **2004**, *108*, 2072. (i) Giorgio, E.; Rosini, C.; Viglione, R. G.; Zanasi, R. *Chem. Phys. Lett.* **2003**, *376*, 452. (j) Giorgio, E.; Viglione, R. G.; Rosini, C. *Tetrahedron*: *Asymmetry* **2004**, *15*, 1979.

10.1021/jo048571n CCC: $27.50
Published on Web 11/16/2004

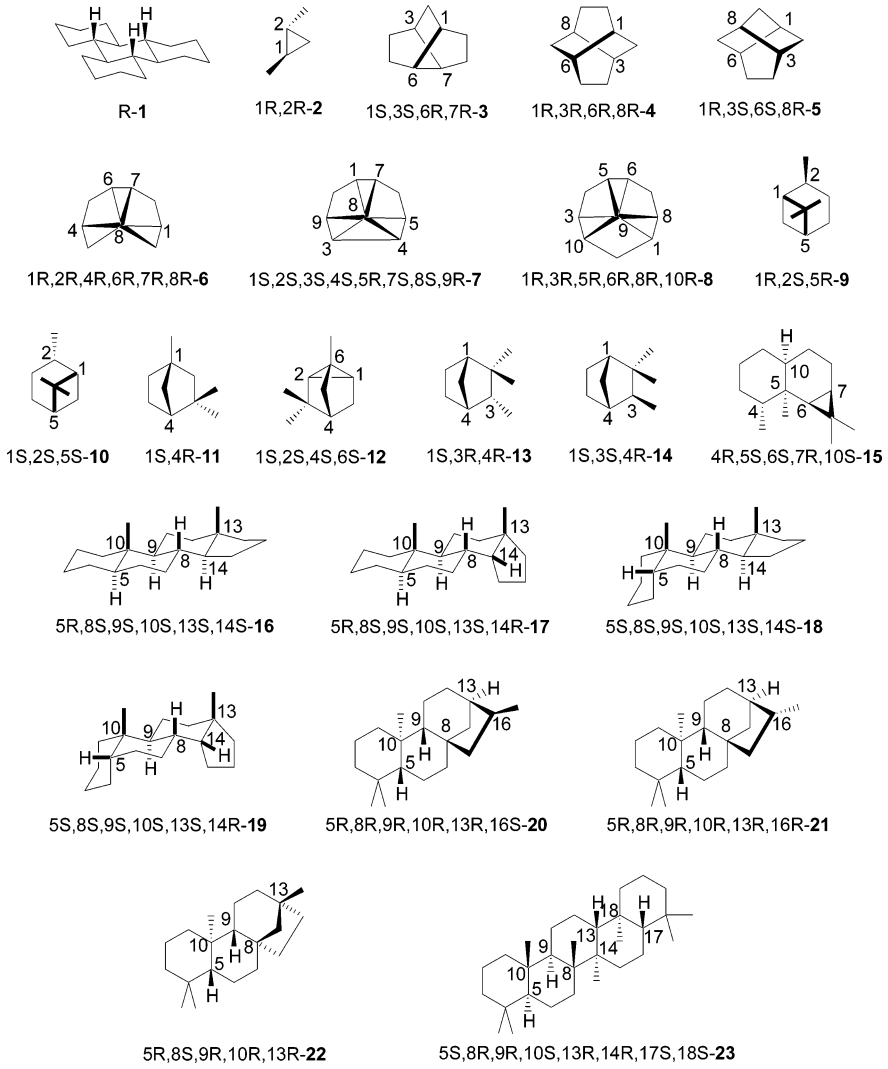

FIGURE 1. Molecules **1**−**23**: **1**, perhydrotriphenylene; **2**, *trans*-1,2-dimethylcyclopropane; **3**, brexane; **4**, twistane; **5**, twist-brendane; **6**, ditwist-brendane; **7**, C_2-bishomocubane; **8**, D_3-trishomocubane; **9**, *cis*-pinane; **10**, *trans*-pinane; **11**, fenchane; **12**, cyclofenchene; **13**, *endo*-isocamphane; **14**, *exo*-isocamphane; **15**, calarane; **16**, 5α,14α-androstane; **17**, 5α,14*β*-androstane; **18**, 5*β*,14α-androstane; **19**, 5*β*,14*β*-androstane; **20**, α-dihydrokaurene; **21**, *β*-dihydrokaurene; **22**, isostevane; and **23**, gammacerane.

This development is particularly valuable for those chiral molecules which do not absorb in the spectral region accessible to ORD and CD spectrometers. Alkanes fall within this category. A large variety of chiral alkanes have been isolated as natural products or synthesized. In many cases their AC's have been firmly established. However, in some cases AC's have not been determined, or the reported AC's appear to be less than secure. The chiral D_3-symmetric alkane *anti-trans-anti-trans-anti-trans*-perhydrotriphenylene (PHTP) (**1**, Figure 1) is a case in point. Optically active PHTP was first synthesized by Farina and Audisio[5] from PHTP-2-carboxylic acid, resolved via fractional crystallography of its dehydroabietylamine salt. Its AC was assigned via calculation of its $[\alpha]_D$ value using an empirical methodology of Brewster.[1c] Subsequently, the AC of PHTP-2-carboxylic acid was assigned via conversion to PHTP-2-one, whose AC was in turn assigned by application of the Octant Rule[1c,d,6] to its UV ORD and CD.[7] The synthesis of PHTP from PHTP-2-carboxylic acid then permitted the AC of PHTP to be assigned, with the same result as obtained earlier. However, the Brewster methodology is not sufficiently reliable to unambiguously assign the AC of PHTP and while the Octant Rule is much more reliable, it is not infallible, as is illustrated by the case of the chiral alkane, twistane [**4**, Figure 1]. First synthesized in optically active form by Adachi et al.,[8] the AC of **4** was assigned by application of the Octant Rule to the CD of the

(4) (a) Stephens, P. J.; Devlin, F. J.; Cheeseman, J. R.; Frisch, M. J.; Rosini, C. *Org. Lett.* **2002**, *4*, 4595. (b) Stephens, P. J.; Devlin, F. J.; Cheeseman, J. R.; Frisch, M. J.; Bortolini, O.; Besse, P. *Chirality* **2003**, *15*, S57. (c) Stephens, P. J.; McCann, D. M.; Butkus, E.; Stoncius, S.; Cheeseman, J. R.; Frisch, M. J. *J. Org. Chem.* **2004**, *69*, 1948. (d) Stephens, P. J.; McCann, D. M.; Devlin, F. J.; Cheeseman, F. J.; Frisch, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 7514. (e) Polavarapu, P. L. *Angew. Chem.* **2002**, *41*, 4544. (f) Wang, F.; Wang, Y.; Polavarapu, P. L.; Li, T.; Drabowicz, J.; Pietrusiewicz, K. M.; Zygo, K. *J. Org. Chem.* **2002**, *67*, 6539.

(5) Farina, M.; Audisio, G. *Tetrahedron Lett.* **1967**, *14*, 1285.

(6) Lightner, D. A. In *Circular Dichroism*: *Principles and Applications*; Berova, N., Nakanishi, K., Woody, R. W., Eds.; Wiley-VCH: New York, 2000; Chapter 10.

(7) Farina, M.; Audisio, G. *Tetrahedron* **1970**, *26*, 1839.

(8) Adachi, K.; Naemura, K.; Nakazaki, M. *Tetrahedron Lett.* **1968**, *9*, 5467.

precursors 6-oxo-methyl ester-bicyclo[2.2.2]octane-2-acetic acid (**24**) and twistan-2-one. Subsequently, Tichy and Sicher[9] reported an alternative synthesis of **4** and confirmed the AC of Adachi et al. by application of the Octant Rule to the CD of the precursor twistan-4-one. Unfortunately, subsequent syntheses of **4** by other routes[10−12] showed the AC of **4** arrived at to be incorrect and, therefore, that the AC's of **24**, twistan-2-one, and twistan-4-one obtained using the Octant Rule were also all incorrect. Since the literature AC of PHTP is based predominantly on the AC of PHTP-2-one, which was assigned using the Octant Rule, it must be concluded that it is subject to some uncertainty.

The general goal of our work is to use TDDFT calculations of specific rotations to assign the AC's of chiral alkanes whose AC's are either unknown or insecure. To determine AC's in this way it is first necessary to calibrate the reliability of the methodology, using a range of alkanes whose specific rotations and AC's are both known. To date, TDDFT calculations of the specific rotations of alkanes have been reported for only two molecules, specifically for *trans*-1,2-dimethylcyclopropane (**2**, Figure 1)[2b] and *cis*-pinane (**9**, Figure 1).[3f] Before proceeding to the study of our target molecules, we have therefore carried out calculations for a range of alkanes to more thoroughly calibrate the performance of the TDDFT methodology. The results of this preliminary study are reported in this paper, together with results for PHTP, **1**, which provide strong support for the previously assigned AC. Further applications will be reported in future publications.

The molecules chosen for study are the chiral alkanes **2**−**23**, shown in Figure 1. As will be demonstrated below, they are all conformationally rigid, i.e., at equilibrium at room temperature they exist essentially exclusively in one conformation. This avoids the complications which ensue in conformationally flexible molecules.[4b] They range in size from *trans*-1,2-dimethylcyclopropane, **2**, containing 5 C atoms, to the triterpane gammacerane, **23**, containing 30 C atoms. For all of these molecules, the sodium D line specific rotations, $[\alpha]_D$, have been reported, except for **23** where $[\alpha]_{546}$ was reported instead. In all cases, AC's have been assigned.

Methods

Conformational analysis of molecules **1**−**23** has been carried out using the following protocol. First, Monte-Carlo conformational searching was carried out using the MMFF94 molecular mechanics force field via the program SPARTAN 02.[13] Second, the conformational structures obtained were further optimized using ab initio Density Functional Theory (DFT), together with the B3LYP functional and the 6-31G* basis set, via the programs SPARTAN 02 or GAUSSIAN 98/03.[14] For molecules **16** and **17**, relaxed Potential Energy Surface (PES) scans were carried out using GAUSSIAN 98/03 with respect to the ring puckering angle of ring D.

Specific rotations, $[\alpha]_\nu$, have been calculated for the lowest energy conformations of molecules **1**−**23**, using TDDFT and GAUSSIAN 03.[14] The methodology[2a−c] uses Gauge-Invariant (Including) Atomic Orbitals, GIAOs, guaranteeing origin-independent rotations.[2a] [Note that GIAOs are not used in all implementations of TDDFT in calculating optical rotations.[2] Specifically, the programs TURBOMOLE[2d,e,15] and ADF[2f,16] do not use GIAOs and yield origin-*dependent* rotations.] The functional and basis set used in calculating specific rotations were B3LYP and aug-cc-pVDZ, respectively. B3LYP is a widely used state-of-the-art hybrid functional. The aug-cc-pVDZ basis set[2a] contains diffuse functions, which have been shown to significantly reduce basis set error in calculated rotations, and provides an optimum compromise between computational time and basis set error.[2a] For selected molecules other functionals and basis sets have also been used, specifically, the B3PW91 and PBE1PBE hybrid functionals and the 6-311++G(2d,2p) and aug-cc-pVTZ basis sets.[2a] Specific rotations were calculated at B3LYP/6-31G* geometries, obtained using GAUSSIAN 98/03. For selected molecules other geometries have also been used, specifically, B3LYP/TZ2P, MP2/6-31G*, and HF/6-31G* geometries.

For two molecules, *cis*- and *trans*-pinane, **9** and **10**, we have examined the magnitude of solvent effects, using seven diverse solvents. The $[\alpha]_D$ values of (+)-*cis*-pinane [Fluka] and (−)-*trans*-pinane [Fluka] were measured in cyclohexane, carbon tetrachloride, benzene, chloroform, acetone, methanol, and acetonitrile at 0.1 M concentrations. Solvent effects were incorporated in the TDDFT calculations of $[\alpha]_D$ using the Polarizable Continuum Model (PCM), as previously described.[2c]

Results

The experimental specific rotations, $[\alpha]_D$, for the molecules **1**−**22** and $[\alpha]_{546}$ for molecule **23** are summarized in Table 1, together with their reported absolute configurations. For some molecules enantiomeric excesses (ee's) were determined simultaneously with the specific rotations, or could be determined retroactively from subsequent data. In these cases, $[\alpha]_D$ values are available for the limit of optical purity (100% ee) and these values are also given in Table 1. In other cases, ee's have not been reported. For molecules which are natural products, or are obtained from natural products, we expect the ee's to be close to 100%. With the one exception of the use of the Brewster methodology for calculating specific rotation to assign the AC of PHTP,[5] Absolute Configurations (AC's) have been determined by chemical correlation, i.e., by connection using reactions of predictable stereochemistry to other molecules of known AC. A useful compendium of AC's determined by chemical correlation is ref 17.

Optically active *anti-trans-anti-trans-anti-trans*-perhydrotriphenylene (PHTP), **1**, was obtained by Farina and Audisio[5,7] from the 2-carboxylic acid derivative, resolved via fractional crystallography of the dehydroabietylamine salt. Chemically pure (−)-**1**, with $[\alpha]_D$ −93 (methyl ethyl ketone), was shown to be optically pure via isotopic dilution.[7] The AC of (−)-**1** was assigned as *R*, initially[5] via calculation of the $[\alpha]_D$ of **1**, using a methodology of Brewster,[1c] and later[7] by chemical correlation

(9) Tichy, M.; Sicher, J. *Tetrahedron Lett.* **1969**, *10*, 4609.
(10) Tichy, M. *Tetrahedron Lett.*, **1972**, *13*, 2001.
(11) Tichy, M. *Collect. Czech. Chem. Commun.* **1974**, *39*, 2673.
(12) Nakazaki, M.; Naemura, K.; Harita, S. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 1907.
(13) *Spartan 02*; Wavefunction Inc.: Irvine, CA.
(14) *Gaussian 98 and 03*: Gaussian, Inc.: Pittsburgh, PA.
(15) *Turbomole*; Quantum Chemistry Group, University of Karlsruhe: Karlsruhe, Germany.
(16) *ADF*; Scientific Computing & Modelling: Amsterdam, The Netherlands.
(17) Klyne, W.; Buckingham, J. *Atlas of Stereochemistry*; *Absolute Configurations of Organic Molecules*; Oxford University Press: New York, 1974; for molecule **1** see p 226, for **2** and **4** see p 48, for **9** and **10** see p 84, for **11** see p 86, for **15** see p 102, for **20**−**22** see p 111, and for **23** see p 121.

TABLE 1. Experimental and Calculated Specific Rotations of Alkanes 1−23

molecule	ref	AC	$[\alpha]_D$[a]	ee (%)	$[\alpha]_D$ (100% ee)[a]	solvent	concn[c]	$[\alpha]_D$ (calcd)[a,b]
1	5, 7	*R*	−93	100	−93	MeCOEt		−119.8
2	19	1*R*,2*R*	−46.0	100	−46.0	diglyme	0.0272	−58.1
3	22, 23	1*S*,3*S*,6*R*,7*R*	−94.3	64.6	−146.0	EtOH	0.214	−106.6
4	8, 24	1*R*,3*R*,6*R*,8*R*	414	94	440	EtOH	0.489	360.4
5	24, 25	1*R*,3*S*,6*S*,8*R*	−235	83	−284	EtOH	0.52	−246.7
6	24, 27	1*R*,2*R*,4*R*,6*R*,7*R*,8*R*	−274	90	−304	$CHCl_3$	0.302	−186.9
7	24, 28	1*S*,2*S*,3*S*,4*S*,5*R*,7*S*,8*S*,9*R*	−33.8	77	−44.0	$CHCl_3$	0.621	−31.7
8	27	1*R*,3*R*,5*R*,6*R*,8*R*,10*R*	155	94	165	$CHCl_3$	0.76	131.9
9	32	1*R*,2*S*,5*R*	21.5	92.3	23.3	neat		17.6
10	32	1*S*,2*S*,5*S*	−14.5	91.3	−15.9	neat		3.6
11	36	1*S*,4*R*	−18.11			EtOH	0.383	−16.0
12	37	1*S*,2*S*,4*S*,6*S*	−0.97	85.0	−1.14			−2.4
13	39	1*S*,3*R*,4*R*	6.3	95.1	6.6	toluene		−11.3
14	39	1*S*,3*S*,4*R*	15.0	95.1	15.8	toluene		4.1
15	41	4*R*,5*S*,6*S*,7*R*,10*S*	−53	82	−65	$CHCl_3$		−42.8
16	43	5*R*,8*S*,9*S*,10*S*,13*S*,14*S*	1.32					14.1
17	43	5*R*,8*S*,9*S*,10*S*,13*S*,14*R*	33.82					62.4
18	43	5*S*,8*S*,9*S*,10*S*,13*S*,14*S*	2.03					6.8
19	43	5*S*,8*S*,9*S*,10*S*,13*S*,14*R*	31.88					48.3
20	45,46	5*R*,8*R*,9*R*,10*R*,13*R*,16*S*	−34.6			$CHCl_3$	0.479	−60.1
21	47,48	5*R*,8*R*,9*R*,10*R*,13*R*,16*R*	−67			$CHCl_3$	1.0	−84.5
22	49	5*R*,8*S*,9*R*,10*R*,13*R*	−3.9			$CHCl_3$	0.51%	−7.2
23	50	5*S*,8*R*,9*R*,10*S*,13*R*,14*R*,17*S*,18*S*	29.4[d]					39.0[a]/46.0[d]

[a] $[\alpha]_D$ in deg·[dm·g/cm^3]$^{-1}$. [b] B3LYP/aug-cc-pVDZ//B3LYP/6-31G*. [c] Concentrations in g/100 mL. [d] $[\alpha]_{546}$.

with PHTP-2-one, whose AC was determined using its UV ORD and CD. Very recently, optically pure enantiomers of **1** have been obtained by chiral gas chromatography of (±)-**1**.[18] For the (−)-enantiomer $[\alpha]_D$ −92.4 (paraldehyde) was reported, in excellent agreement with the earlier value.

Optically active *trans*-1,2-dimethylcyclopropane, **2**, was first synthesized by Doering and Kirmse[19] and its AC assigned via chemical correlation. Doering and Kirmse reported $[\alpha]_D$ −46.0 (diethyleneglycol dimethyl ether, diglyme) for optically pure (−)-**2**. Subsequent measurements have given $[\alpha]_D$ −42 (pentane)[20] and $[\alpha]_D$ −46 (heptane).[21]

Optically active brexane, **3**, was first synthesized by Nakazaki et al.[22] Its AC was deduced (1) via chemical correlation and (2) using the CD of the precursor brexan-2-one. The ee of **3**, $[\alpha]_D$ −94.3 (EtOH), can be estimated using the $[\alpha]_D$ of the precursor brexan-2-one, −201 (EtOH), together with the value, +311 (EtOH), established subsequently for the optically pure (+)-enantiomer.[23] The resulting ee, 64.6%, leads to $[\alpha]_D$ −146.0 (EtOH) for optically pure (−)-**3**.

Optically active twistane, **4**, was first synthesized by Adachi et al.[8] Its AC was established using the CD of the precursors **24** and twistan-2-one. Tichy and Sicher[9] subsequently synthesized optically active **4** and established its AC using the CD of the precursor twistan-4-one, with the same result. However, the AC obtained was subsequently shown by Tichy[10,11] and Nakazaki et al.[12] to be incorrect using chemical correlation. The $[\alpha]_D$ value of optically pure (+)-**4**, 440 (EtOH), was obtained by Nakazaki et al.[24] via NMR of the acetate derivative of an alcohol from which twistan-2-one was synthesized, establishing the ee of the twistan-2-one previously used to synthesize (+)-**4**.[8]

Optically active twist-brendane, **5**, was first synthesized by Naemura and Nakazaki.[25] Its AC was established, and subsequently confirmed,[12] via chemical correlation. Multiple values of $[\alpha]_D$ have been published.[12,25,26] Nakazaki et al.[24] arrived at $[\alpha]_D$ −284 (99% EtOH) for optically pure (−)-**5**, using the measured $[\alpha]^{25}_D$ together with the ee of the precursor (−)-*endo*-5-carboxylic acid-norborn-5-ene.

Optically active ditwist-brendane, **6**, was first synthesized by Nakazaki et al.[27] Its AC was deduced via chemical correlation. Subsequently, synthesis from *exo*-ditwist-brendan-2-ol, the ee of whose acetate derivative was determined using NMR, allowed the $[\alpha]_D$ of optically pure (−)-**6**, −304 ($CHCl_3$), to be determined.[24]

Optically active C_2-bishomocubane, **7**, was first synthesized by Nakazaki and Naemura.[28] Its AC was assigned by correlation to a related ketone whose AC was determined from its CD. The $[\alpha]_D$ value of optically pure (−)-**7**, −44 ($CHCl_3$), was obtained[24] via conversion of **7** to **6**,[27] whose maximum rotation had been established (see above).

Optically active D_3-trishomocubane, **8**, was first synthesized by Nakazaki et al.[27] and Eaton and Leipzig.[29] Its AC was assigned via the CD of precursor D_3-trishomocubanones. The $[\alpha]_D$ value of optically pure (+)-**8**, +165 ($CHCl_3$), was obtained[27] using NMR to determine the ee of the acetate derivative of a precursor alcohol.

(18) Schürch, S.; Saxer, A.; Claude, S.; Tabacchi, R.; Trusch, B.; Hulliger, J. *J. Chromatogr. A* **2001**, *905*, 175.
(19) Doering, W. v. E.; Kirmse, W. *Tetrahedron* **1960**, *11*, 272.
(20) Moore, W. R.; Anderson, H. W.; Clark, S. D.; Ozretich, T. M. *J. Am. Chem. Soc.* **1971**, *93*, 4932.
(21) Fry, A. J.; Britton, W. E. *J. Org. Chem.* **1973**, *38*, 4016.
(22) Nakazaki, M.; Naemura, K.; Kadowaki, H. *J. Org. Chem.* **1976**, *41*, 3725.
(23) Nakazaki, M.; Chikamatsu, H.; Naemura, K.; Nishino, M.; Murakami, H.; Asao, M. *J. Org. Chem.*, **1979**, *44*, 4588.
(24) Nakazaki, M.; Naemura, K.; Nakahara, S. *J. Org. Chem.* **1978**, *43*, 4745.
(25) Naemura, K.; Nakazaki, M. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 888.
(26) Nakazaki, M.; Naemura, K. *J. Org. Chem.* **1977**, *42*, 4108.
(27) Nakazaki, M.; Naemura, K.; Arashiba, N. *J. Org. Chem.* **1978**, *43*, 689.
(28) Nakazaki, M.; Naemura, K. *J. Org. Chem.* **1977**, *42*, 2985.
(29) Eaton, P. E.; Leipzig, B. *J. Org. Chem.* **1978**, *43*, 2483.

cis-Pinane, **9**, and *trans*-pinane, **10**, are well-known monoterpenes,[30] commercially available from Fluka. Their AC's have been established via chemical correlations.[17,31] Zweifel and Brown[32] obtained (−)-*cis*-pinane, $[\alpha]_D$ −19.3 (neat), and (−)-*trans*-pinane, $[\alpha]_D$ −14.5 (neat), from (−)-*β*-pinene, $[\alpha]_D$ −21.1 (neat), and also obtained (+)-*cis*-pinane, $[\alpha]_D$ +21.5 (neat), from (+)-α-pinene, $[\alpha]_D$ +47.6 (neat). Using $[\alpha]_D$ +51.6 (neat) for 100% ee (+)-α-pinene[33] and $[\alpha]_D$ +23.1 (neat) for 100% ee (+)-*β*-pinene,[34] the $[\alpha]_D$ values of (−)- and (+)-*cis*-pinane can be corrected to −21.1 and +23.3, respectively. The larger of these values provides the best estimate of the $[\alpha]_D$ of optically pure neat *cis*-pinane, and is in excellent agreement with the Fluka values of −24 [≥97% purity] and +24 [≥99% purity] for (−)- and (+)-*cis*-pinane, respectively.[35] Correction for (−)-*trans*-pinane gives $[\alpha]_D$ −15.9 (neat), also in excellent agreement with Fluka values of −17 [∼99% purity] and +17 [≥95% purity, ≥97% ee] for (−)- and (+)-*trans*-pinane.[35]

The AC of the monoterpene fenchane, **11**, has been established via chemical correlations.[17,31] The $[\alpha]_D$ of optically pure fenchane does not appear to have been reliably established. The largest literature value we have found is −18.1 (ethanol)[36] and we take this to be the best estimate.

The AC of the monoterpene cyclofenchene, **12**, has been established via chemical correlations.[31] Its $[\alpha]_D$ value is very small. Hückel and Kern[37] reported $[\alpha]_D$ −0.97 for (−)-**12** synthesized from (+)-*endo*-fenchyl acetate of $[\alpha]_D$ +59.1. Using $[\alpha]_D$ +69.5 as the maximum rotation of the latter,[38] we estimate an ee of 85.0% for the (−)-**12** of Hückel and Kern and, thence, $[\alpha]_D$ −1.14 for optically pure **12**.

endo-Isocamphane, **13**, and *exo*-isocamphane, **14**, are monoterpenes obtained by hydrogenation of camphene, a reaction which establishes their AC's. Vereschchagina et al.[39] obtained *endo*- and *exo*-isocamphanes of $[\alpha]_D$ +6.3 (toluene) and +15.0, respectively, starting from (−)-camphene of $[\alpha]_D$ −111.8. Since (−)-camphene has the 1*S*,4*R* AC,[17,31] (+)-endoisocamphane and (+)-exoisocamphane have the 1*S*,3*R*,4*R* and 1*S*,3*S*,4*R* AC's, respectively. Using $[\alpha]_D$ −117.5 (toluene) for optically pure (−)-camphene,[40] we estimate $[\alpha]_D$ values for optically pure (+)-*endo*- and (+)-*exo*-isocamphane of 6.6 and 15.8, respectively.

The AC of the sesquiterpene calarane, **15**, has been established via chemical correlations.[17] Büchi et al.[41] reported $[\alpha]_D$ −53 ($CHCl_3$) for (−)-**15** obtained from (+)-calarene with $[\alpha]_D$ +58 (EtOH). Rienäcker and Graefe reported $[\alpha]_D$ +70.9 for (+)-calarene.[42] We obtain thence a corrected $[\alpha]_D$ for (−)-**15** of −65.

Allinger and Wu[43] reported the $[\alpha]_D$ values of the four isomeric androstanes, **16**−**19**, exhibiting 5α,14α, 5α,14*β*, 5*β*,14α, and 5*β*,14*β* stereochemistries, respectively. Their AC's are defined via their synthesis from naturally occurring steroids of known stereochemistry. The reported $[\alpha]_D$ values range from 1.3 to 33.8. Optical purities were not reported.

The AC's of the diterpenes α-dihydrokaurene (stevane A, kaurane), **20**, *β*-dihydrokaurene (stevane B), **21**, and isostevane (stachane, beyerane), **22**, have been established via chemical correlations.[17] The $[\alpha]_D$ values reported for **20** have been generally in the range 30−35 ($CHCl_3$).[44] The value of Pelletier et al. is −34.6 ($CHCl_3$) for (−)-**20**[45,46] and we take this as the best estimate for optically pure **20**. Two independent groups[47,48] reported $[\alpha]_D$ −67 ($CHCl_3$) for **21** and we adopt this value for optically pure **21**. The $[\alpha]_D$ of **22** is very small. We use the largest value of Kapadi and Dev:[49] −3.9 ($CHCl_3$).

The AC of the triterpene gammacerane (tetrahymane), **23**, has been established via chemical correlations.[17] The $[\alpha]_{546}$ of **23** of >99% chemical purity was reported to be +29.4.[50]

Before calculating the $[\alpha]_D$ values for **1**−**23** it is necessary to obtain their equilibrium structures and, in the case of molecules which are conformationally flexible, to verify that only one conformation is significantly populated at room temperatures. For all molecules, we have initially carried out a Monte-Carlo conformational search using the MMFF94 molecular mechanics force field to define the structures and relative energies of the conformations lying within 10 kcal/mol of the lowest energy conformation. The MMFF94 structures obtained are re-optimized using DFT at the B3LYP/6-31G* level to obtain the relative B3LYP/6-31G* energies of all conformations. The molecule is defined as "conformationally rigid" if there are no conformations whose B3LYP/6-31G* energies are within 2 kcal/mol of the lowest energy conformation. For molecules where conformations exist at <10 kcal/mol at the MMFF94 level, MMFF94 and B3LYP/6-31G* relative energies are given in Table 2. All molecules are confirmed to be rigid. In the cases of molecules **16** and **17** we have further examined the conformational flexibility of ring D, with rings A, B, and C in chair conformations, via PES scanning. Relaxed PES scans with respect to the ring puckering angle confirm that only one stable conformation of this cyclopentane ring exists (see Supporting Information).

TDDFT/GIAO $[\alpha]_D$ values calculated at the B3LYP/6-31G* equilibrium geometries of the lowest energy

(30) Erman, W. F. *Chemistry of the Monoterpenes*; Marcel Dekker: New York, 1985.
(31) Reference 30, Chapter 3, pp 127−328.
(32) Zweifel, G.; Brown, H. C. *J. Am. Chem. Soc.* **1964**, *86*, 393.
(33) Brown, H. C.; Jadhav, P. K.; Desai, M. C. *J. Org. Chem.* **1982**, *47*, 4583.
(34) Brown, H. C.; Zaidlewicz, M.; Bhat, K. S. *J. Org. Chem.* **1989**, *54*, 1764.
(35) *Catalogue of Laboratory and Analytical Reagents*; Fluka Chemical Corp.: Milwaukee, WI, 2001/2002.
(36) Wolff, L. *Justus Liebigs Ann. Chem.* **1912**, *394*, 97.
(37) Hückel, W.; Kern, H.-J. *Justus Liebigs Ann. Chem.* **1965**, *687*, 40.
(38) Hirsjaervi, P. *Ann. Acad. Sci. Fenn. Ser. A2* **1957**, *84*, 10.
(39) Vereshchagina, A. A.; Sapteeva, T. I.; Slivkin, L. G.; Garmashov, V. I.; Rudakov, G. A. *J. Appl. Chem. USSR* **1982**, *55*, 409.
(40) Bain, J. P.; Best, A. H.; Hampton, B. L.; Hawkins, G. A.; Kitchen, L. J. *J. Am. Chem. Soc.* **1950**, *72*, 3124.
(41) Büchi, G.; Greuter, F.; Tokoroyama, T. *Tetrahedron Lett.* **1962**, *18*, 827.
(42) Rienäcker, R.; Graefe, J. *Angew. Chem.* **1985**, *97*, 348.
(43) Allinger, N. L.; Wu, F. *Tetrahedron* **1971**, *27*, 5093.
(44) *CrossFire Beilstein Database*; MDL Information Systems GmbH: Frankfurt, Germany, 2004.
(45) Pelletier, S. W.; Desai, H. K.; Finer-Moore, J.; Mody, N. V. *J. Am. Chem. Soc.* **1979**, *101*, 6741.
(46) Pelletier, S. W.; Mody, N. V.; Desai, H. K. *J. Org. Chem.* **1981**, *46*, 1840.
(47) Briggs, L. H.; Cain, B. F.; Cambie, R. C.; Davis, B. R.; Rutledge, P. S.; Wilmshurst, J. K. *J. Chem. Soc.* **1963**, 1345.
(48) Mossettig, E.; Beglinger, U.; Dolder, F.; Lichti, H.; Quitt, P.; Waters, J. A. *J. Am. Chem. Soc.* **1963**, *85*, 2305.
(49) Kapadi, A. H.; Dev, S. *Tetrahedron Lett.* **1964**, *38*, 2751.
(50) Hills, I. R.; Whitehead, E. V.; Anders, D. E.; Cummins, J. J.; Robinson, W. E. *Chem. Commun.* **1966**, 752.

TABLE 2. Conformational Analysis of Alkanes 1 and 15−23

molecule	conf[a]	$\Delta E^{b,c}$	$\Delta E^{b,d}$	molecule	conf[a]	$\Delta E^{b,c}$	$\Delta E^{b,d}$
1[e]	CCC	0.00	0.00	**19**[f]	CCC	0.00	0.00
	CCB	4.72	4.28		CCB	5.02	2.77
	CBB	9.94	10.07		BCC	5.60	4.72
					CCB	7.09	5.26
					CBC	7.42	6.46
					BCC	8.33	8.10
15	CB	0.00	0.00	**20**	CCC	0.00	0.00
	BB	4.21	4.30		BCC	2.70	3.41
	BB	5.93	4.86		CBB	6.87	6.34
	CC	7.46	6.23				
16[f]	CCC	0.00	0.00	**21**	CCC	0.00	0.00
	CCC	6.26	5.76		BCC	2.64	3.16
					CBB	6.23	5.66
17[f]	CCC	0.00	0.00	**22**	CCC	0.00	0.00
	CCB	5.06	2.94		BCC	3.21	3.20
	BCC	6.14	5.56		BCC	9.95	7.91
	CCB	7.20	4.98				
18[f]	CCC	0.00	0.00	**23**	CCCCC	0.00	0.00
	BCC	5.73	4.38		CCCCB	3.25	3.48
	CBC	6.54	4.94		BCCCB	6.54	6.68
	BCC	8.56	7.84				

[a] C = chair, B = boat/twist-boat. [b] Units: kcal/mol. [c] MMFF94. [d] B3LYP/6-31G*. [e] Central ring in a chair conformation. [f] Conformations refer to rings A, B, and C.

conformations of **2**−**22** using the functional B3LYP and the aug-cc-pVDZ basis set are given in Table 1 and compared to experimental $[\alpha]_D$ values in Figure 2. Qualitatively, the overall correlation of calculated and experimental $[\alpha]_D$ values is very good. Quantitatively, experimental $[\alpha]_D$ values range from −304 to +440. Differences of calculated and experimental $[\alpha]_D$ values range from 1 to 117. The average absolute deviation is 24.8. For several molecules of the set **2**−**22** experimental $[\alpha]_D$ values are small. For nine molecules, $[\alpha]_D$ values are <30. Given an average deviation of 24.8, one would expect calculated $[\alpha]_D$ values for some of these molecules to be of opposite sign to experimental $[\alpha]_D$ values. This is indeed the case: for two molecules, **10** and **13**, calculated $[\alpha]_D$ values are incorrect in sign, while deviating from experimental $[\alpha]_D$ values by an amount less than the average deviation. As discussed further below, this finding is of considerable significance with regard to the application of calculated $[\alpha]_D$ values to the determination of AC's.

The calculation for **2** correctly predicts the sign of $[\alpha]_D$. The difference between calculated and experimental $[\alpha]_D$ values is 12.1, much less than the average deviation for **2**−**22**.

The calculations for the six gyrochiral alkanes, **3**−**8**, correctly predict the signs of $[\alpha]_D$ in all cases. Quantitatively, the difference between calculated and experimental $[\alpha]_D$ values varies widely, ranging from 12.3 (for **7**) to 117.1 (for **6**). With the exception of **7**, deviations are all greater than the average deviation for **2**−**22**. The average of the absolute values of the deviations for **3**−**8** is 53.1.

The calculations for **9** and **10** predict the correct sign of $[\alpha]_D$ for **9** and the incorrect sign for **10**. The differences between calculated and experimental $[\alpha]_D$ values are 5.7 and 19.5, respectively; both deviations are less than the average deviation for **2**−**22**. For **11** and **12** agreement is excellent, in both sign and magnitude: the differences between calculated and experimental $[\alpha]_D$ are 2.1 and 1.3, respectively. For **13** and **14**, the calculated signs of $[\alpha]_D$ are incorrect and correct, respectively. The differences between calculated and experimental $[\alpha]_D$ values are 17.9 and 11.7, respectively, both less than the average deviation for **2**−**22**.

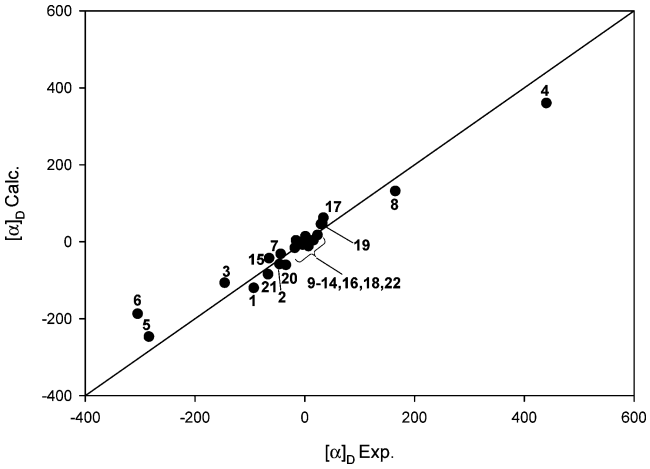

FIGURE 2. Comparison of calculated and experimental $[\alpha]_D$ values of **1**−**22**. The line has slope +1.

The calculated $[\alpha]_D$ for **15** is correct in sign; it differs in magnitude from the experimental $[\alpha]_D$ by 22, slightly less than the average deviation for **2**−**22**.

The calculations for the four androstanes, **16**−**19**, correctly predict the sign of $[\alpha]_D$ for all four isomers and, further, the qualitative variations in $[\alpha]_D$ with stereochemistry at positions C5 and C14. The 5α,14*β* and 5*β*,14*β* isomers exhibit much larger $[\alpha]_D$ values (62.4 and 48.3, respectively) than the 5α,14α and 5*β*,14α isomers (14.1 and 6.8, respectively), as observed. Quantitatively, the agreement is better than average for the 5α,14α, 5*β*,14α, and 5*β*,14*β* isomers; for 5α,14*β*-androstane the difference between calculated and experimental $[\alpha]_D$ values is a little above average (28.6).

The calculations for the two dihydrokaurenes, **20** and **21**, correctly predict the signs of $[\alpha]_D$ and, further, the greater magnitude of $[\alpha]_D$ for the *β*-epimer. Quantitatively, for both **20** and **21** the difference between calculated and experimental $[\alpha]_D$ values is close to the average deviation. For **22**, the sign of $[\alpha]_D$ is correctly predicted; the magnitude differs from the experimental $[\alpha]_D$ by 3.3.

For **23** we have calculated both $[\alpha]_D$ and $[\alpha]_{546}$, with the results given in Table 1. As to be expected, $[\alpha]_{546}$ is a little larger than $[\alpha]_D$. The calculated $[\alpha]_{546}$ agrees in sign with the experimental value. The difference between calculated and experimental $[\alpha]_{546}$ values is 16.6, less than the average error in $[\alpha]_D$ for **2**−**22**.

We have explored the sensitivity of predicted $[\alpha]_D$ values to the choice of equilibrium geometry and of the density functional and basis set used in calculating $[\alpha]_D$ for molecules **6**, **9**, **10**, **13**, and **14**, with the results given in Table 3. The additional geometries used are B3LYP/TZ2P, HF/6-31G*, and MP2/6-31G*. The additional functionals used are B3PW91 and PBE1PBE. The additional basis sets used are 6-311++G(2d,2p) and aug-cc-pVTZ. For **9**, the predicted $[\alpha]_D$ varies from 15.4 to 19.8, while for **10** the variation is from 2.4 to 6.8. For **13** and **14** the ranges are −1.5 to −11.8 and 4.1 to 11.3. For **6**, $[\alpha]_D$ varies from −173.0 to −186.9. The variations in all five

TABLE 3. Dependence of Calculated Specific Rotations for Alkanes 6, 9, 10, 13, and 14 on Density Functional, Basis Set, and Equilibrium Geometry

molecule	geometry	functional	basis set	$[\alpha]_D$
6	B3LYP/6-31G*	B3LYP	aug-cc-pVDZ	−186.9
	B3LYP/6-31G*	B3PW91	aug-cc-pVDZ	−183.3
	B3LYP/6-31G*	PBE1PBE	aug-cc-pVDZ	−181.7
	B3LYP/6-31G*	B3LYP	6-311++G(2d,2p)	−173.0
	MP2/6-31G*	B3LYP	aug-cc-pVDZ	−183.6
	B3LYP/TZ2P	B3LYP	aug-cc-pVDZ	−184.1
	HF/6-31G*	B3LYP	aug-cc-pVDZ	−180.0
9	B3LYP/6-31G*	B3LYP	aug-cc-pVDZ	17.6
	B3LYP/6-31G*	B3PW91	aug-cc-pVDZ	16.1
	B3LYP/6-31G*	PBE1PBE	aug-cc-pVDZ	16.2
	B3LYP/6-31G*	B3LYP	6-311++G(2d,2p)	15.4
	B3LYP/6-31G*	B3LYP	aug-cc-pVTZ	15.5
	MP2/6-31G*	B3LYP	aug-cc-pVDZ	19.8
	B3LYP/TZ2P	B3LYP	aug-cc-pVDZ	17.1
	HF/6-31G*	B3LYP	aug-cc-pVDZ	18.6
10	B3LYP/6-31G*	B3LYP	aug-cc-pVDZ	3.6
	B3LYP/6-31G*	B3PW91	aug-cc-pVDZ	4.2
	B3LYP/6-31G*	PBE1PBE	aug-cc-pVDZ	3.9
	B3LYP/6-31G*	B3LYP	6-311++G(2d,2p)	3.2
	B3LYP/6-31G*	B3LYP	aug-cc-pVTZ	2.5
	MP2/6-31G*	B3LYP	aug-cc-pVDZ	2.4
	B3LYP/TZ2P	B3LYP	aug-cc-pVDZ	4.1
	HF/6-31G*	B3LYP	aug-cc-pVDZ	6.8
13	B3LYP/6-31G*	B3LYP	aug-cc-pVDZ	−11.3
	B3LYP/6-31G*	B3PW91	aug-cc-pVDZ	−11.0
	B3LYP/6-31G*	PBE1PBE	aug-cc-pVDZ	−11.3
	B3LYP/6-31G*	B3LYP	6-311++G(2d,2p)	−11.6
	MP2/6-31G*	B3LYP	aug-cc-pVDZ	−1.5
	B3LYP/TZ2P	B3LYP	aug-cc-pVDZ	−11.8
	HF/6-31G*	B3LYP	aug-cc-pVDZ	−6.7
14	B3LYP/6-31G*	B3LYP	aug-cc-pVDZ	4.1
	B3LYP/6-31G*	B3PW91	aug-cc-pVDZ	5.6
	B3LYP/6-31G*	PBE1PBE	aug-cc-pVDZ	5.4
	B3LYP/6-31G*	B3LYP	6-311++G(2d,2p)	8.3
	MP2/6-31G*	B3LYP	aug-cc-pVDZ	11.3
	B3LYP/TZ2P	B3LYP	aug-cc-pVDZ	2.7
	HF/6-31G*	B3LYP	aug-cc-pVDZ	9.9

molecules are very similar in magnitude, ranging from 4.4 (**9** and **10**) to 13.9 (**6**). In no case is the sign changed.

We have explored the solvent dependence of $[\alpha]_D$, both experimentally and theoretically, for (+)-**9** and (−)-**10** and for a set of seven, chemically diverse solvents, with the results shown in Table 4. Experimentally, the solvent dependence is small for both **9** and **10**; the variation is 6.2 and 9.3, respectively. The solvent dependence of $[\alpha]_D$ has been calculated using the PCM, as described previously.[2c] For both **9** and **10** the variation is also small: 0.8 and 1.3, respectively.

Discussion

In an earlier study, we reported TDDFT/GIAO B3LYP/aug-cc-pVDZ calculations of $[\alpha]_D$ values for 28 chiral organic molecules of widely varying structure.[2b] For this set of molecules, the average absolute deviation between calculated and experimental $[\alpha]_D$ values was 23.1; the maximum deviation was 70. Only one of the 28 molecules was an alkane: *trans*-1,2-dimethylcyclopropane, **2**. In this work, we have extended the earlier study to a further 20 alkanes **3**−**22**. Comparison between calculated and experimental $[\alpha]_D$ values for the alkane set **2**−**22** finds very similar overall agreement to that for the earlier set of 28 molecules. The average absolute deviation between calculated and experimental $[\alpha]_D$ values is 24.8, a very similar accuracy to that found earlier. However, the largest deviation is 117, for ditwist-brendane, **6**, a deviation much larger than any observed in the earlier study. In addition, for two molecules, *trans*-pinane, **10**, and *endo*-isocamphane, **13**, the predicted $[\alpha]_D$ values are of the wrong sign. In the earlier study, B3LYP/aug-cc-pVDZ calculations were uniformly of the correct sign.

TABLE 4. Solvent Dependence of $[\alpha]_D$ for *cis*-Pinane, 9, and *trans*-Pinane, 10

		$[\alpha]^{25}_D$	
molecule	solvent[a]	expt[b]	calcd[b]
9[c]	gas		17.6
	C_6H_{12}	19.9	16.5
	CCl_4	22.8	16.5
	C_6H_6	23.0	16.6
	$CHCl_3$	20.1	16.8
	$(CH_3)_2CO$	18.4	17.5
	CH_3OH	19.3	17.3
	CH_3CN	16.8	17.2
10[d]	gas		3.6
	C_6H_{12}	−12.6	2.5
	CCl_4	−17.4	1.6
	C_6H_6	−17.0	2.1
	$CHCl_3$	−15.2	2.5
	$(CH_3)_2CO$	−11.2	2.9
	CH_3OH	−10.7	2.8
	CH_3CN	−8.1	2.4

[a] Concentration 0.014 g/mL (0.1 M). [b] All $[\alpha]_D$ values are in deg·[dm·cm^3]$^{-1}$. All calculations were carried out with the PCM methodology, together with the B3LYP functional and the aug-cc-pVDZ basis set. [c] (1R,2S,5R)-*cis*-Pinane, Fluka. [d] (1S,2S,5S)-*trans*-Pinane, Fluka.

As discussed earlier,[2b] there are multiple possible origins of discrepancies between calculated and experimental $[\alpha]_D$ values. Calculational errors can arise from inaccuracies in the equilibrium geometry, and in the density functional and basis set used for the calculation of $[\alpha]_D$. In addition, neither solvent effects nor vibrational effects are included in the calculations. Experimental errors can arise from uncertainties in ee values and from the presence of chemical impurities. In previous studies of 6,8-dioxabicyclo[3.2.1]octanes[3a] and 2,7,8-trioxabicyclo-[3.2.1]octanes[3b] we have found calculated $[\alpha]_D$ values to be insensitive to variations in the ab initio method used to obtain the equilibrium geometry, to the specific hybrid functional used to calculate $[\alpha]_D$, and to a change in basis set from aug-cc-pVDZ to either aug-cc-pVTZ or 6-311++G-(2d,2p). Nevertheless, to further confirm the generality of these findings, we have examined the sensitivity of $[\alpha]_D$ to the choice of equilibrium geometry, functional, and basis set for the specific cases for **6**, **9**, **10**, **13**, and **14**. For **9**, **10**, **13**, and **14** it is of particular interest to examine whether the sign of predicted $[\alpha]_D$ values varies. In the case of **6**, the magnitude of the variation in $[\alpha]_D$ is of primary interest. Our results (summarized in Table 3) show that, for all five molecules, the predicted $[\alpha]_D$ values are very insensitive to the choice of equilibrium geometry, and to the functional and basis set used in calculating $[\alpha]_D$. The variations in geometry, functional, and basis set are limited: only reasonable ab initio geometries have been studied, functionals are limited to hybrid functionals, and the basis sets are all large basis sets incorporating diffuse functions.[2a] Nevertheless, the results obtained lead to the conclusion that uncertainties in these parameters are not likely to constitute the dominant source of error in our calculated $[\alpha]_D$ values. In particular, they do not appear to be the source either of the incorrect signs

of $[\alpha]_D$ predicted for **10** and **13** or of the large error in $[\alpha]_D$ predicted for **6**.

Vibrational effects are not included in our calculations and could contribute significantly to the errors in calculated [α] values.[51] Unfortunately, calculations of vibrational contributions to [α] for **1**−**23** are impractical at this time (possibly excepting **2**) and we can only speculate on the magnitude of such effects. We note, however, that the molecules exhibiting the largest differences between calculated and experimental [α] values, namely the gyrochiral alkanes **3**−**8**, are among the most rigid of the set **1**−**23** as gauged by the magnitudes of their lowest vibrational frequencies. For **3**−**8**, the lowest frequencies are in the range 212−395 cm^{-1}, compared to values in the range 32−206 cm^{-1} for molecules **1**, **2**, and **9**−**23**. There is thus no obvious sign of correlation between the magnitude of the error in the calculation of [α] and the rigidity of the molecule.

Solvent effects are not included in our calculations and could also contribute significantly to the errors in calculated [α] values. We have not found any systematic studies of the solvent dependence of the [α] values of any of molecules **1**−**23**. We have therefore examined the solvent dependence of $[\alpha]_D$ for **9** and **10**, using a set of seven, chemically diverse solvents, with the results given in Table 4. The overall variation for **9** and **10** lies in the range 5−10, consistent with the prediction of small variations predicted by the PCM methodology.[2c] We conclude that solvent effects probably do contribute significantly to the errors in the calculated [α] values of **1**−**23**. However, they are unlikely to be the dominant contribution.

Our work has two goals: first, to evaluate the quantitative accuracy of TDDFT/GIAO calculations of $[\alpha]_D$ values of alkanes and, second, to assess the utility of TDDFT/GIAO calculations of $[\alpha]_D$ in determining the AC's of alkanes. We turn now to the second of these issues. By definition, the AC of a chiral molecule specifies the relation between its absolute stereochemistry and the sign of its specific rotation. The primary requirement of a calculational methodology, if it is to be used to determine AC's, is therefore that it correctly predicts the *sign* of the rotation. With respect to this criterion our B3LYP/aug-cc-pVDZ calculations are successful in 19 out of the 21 molecules **2**−**22**, but unsuccessful for two molecules: **10** and **13**. Thus, the TDDFT/GIAO methodology is not perfect. The incorrect sign predictions for **10** and **13** are not surprising, when one considers the numerical accuracy of the $[\alpha]_D$ predictions for **2**−**22**. For a variety of reasons, as discussed above, the methodology being used does not—and, in fact, cannot—yield $[\alpha]_D$ values in perfect quantitative agreement with experiment. There is therefore a level of error in the TDDFT/GIAO $[\alpha]_D$ predictions. Statistically, for the set **2**−**22**, the average error is in the range 20−30. It follows that for molecules whose predicted $[\alpha]_D$ value is comparable to or less than the methodological error, we cannot predict the sign of $[\alpha]_D$ with certainty. In the cases of (1*S*,2*S*,5*S*)-**10** and (1*S*,3*R*,4*R*)-**13**, predicted $[\alpha]_D$ values are 3.6 and −11.3, respectively. Given an error of ±(20−30), these results clearly lead to the conclusion that the signs of $[\alpha]_D$ and, hence, the predicted AC's for **10** and **13** are indeterminate. The fact that the experimental values, −15.9 and +6.6, are opposite in sign to the predicted values is then not at all surprising. This argument further leads to the conclusion that for all those molecules whose predicted $[\alpha]_D$ values are $\lesssim$30, the sign of $[\alpha]_D$ is likewise indeterminate. *cis*-Pinane, **9**, fenchane, **11**, cyclofenchene, **12**, *exo*-isocamphane, **14**, 5α,14α-androstane, **16**, 5*β*,14α-androstane, **18**, and isostevane, **22**, are in this category. Despite the successful prediction of the sign of $[\alpha]_D$ for all these molecules, allowing for the methodological error level, the signs are in reality indeterminate.

On the other hand, for the molecules whose $[\alpha]_D$ values are significantly larger than the calculational error, comparison of calculated and experimental $[\alpha]_D$ values reliably defines the AC. Thus, for *trans*-1,2-dimethylcyclopropane, **2**, the gyrochiral molecules, **3**−**8**, calarane, **15**, the 5α,14*β*- and 5*β*,14*β*-androstanes, **17** and **19**, and the α- and *β*-dihydrokaurenes, **20** and **21**, our calculations provide strong support for the literature AC's of these molecules. The AC's of all these molecules have been established via chemical correlation with molecules of known AC. In the majority of cases, the AC's of these latter molecules are unimpeachable and there can be no reasonable doubt at this time of the reliability of the AC's of the corresponding alkanes. For example, it would be extremely surprising if the AC's of the terpenes **15**, **20**, and **21** and of the steroids **17** and **19** were incorrect. However, in the case of the gyrochiral molecules **3**−**8** our calculations significantly enhance the security of their AC's.

In the case of gammacerane, **23**, the reported specific rotation is for 546 nm. We are not able to evaluate statistically the accuracy of calculated $[\alpha]_{546}$ values, as we have for $[\alpha]_D$ values, since experimental $[\alpha]_{546}$ values are much less commonly reported. However, since 546 nm is close to the sodium D line wavelength, 589.3 nm, both calculated and experimental $[\alpha]_{546}$ values will certainly be very similar to $[\alpha]_D$ values, being slightly larger due to the shorter wavelength. We expect therefore that the average error in $[\alpha]_{546}$ values for **2**−**22** would be a little larger than that for $[\alpha]_D$ values. For **23**, the difference between the calculated and experimental $[\alpha]_{546}$ values is smaller than the $[\alpha]_D$ error for **2**−**22**. The calculated $[\alpha]_{546}$ value is 46, somewhat larger than the average error. The calculation of $[\alpha]_{546}$ thus supports the literature AC for gammacerane.

We return now to the case of PHTP, **1**. As discussed above, the $[\alpha]_D$ value of optically pure (−)-**1** has been found to be −93 in methyl ethyl ketone.[7] The B3LYP/aug-cc-pVDZ $[\alpha]_D$ value for *R*-**1** is −120 (Table 1). It follows that the AC of **1** is *S*(+)/*R*(−). The difference between calculated and experimental $[\alpha]_D$ values is 27, comparable to the average deviation for **2**−**22**, supporting the reliability of the calculation for **1**. If the AC were in fact *S*(−)/*R*(+), our calculated $[\alpha]_D$ would differ from the experimental $[\alpha]_D$ by 213, enormously larger than the average deviation for **2**−**22**. The probability that our assignment of the AC of **1** is incorrect is thus very small. As discussed above, the literature AC of **1** rests on (1) a calculation of $[\alpha]_D$ using Brewster's methodology[5] and (2) the assignment of the AC of PHTP-2-one, using the Octant Rule and the UV ORD and CD.[7] Both methods led to the AC *S*(+)/*R*(−). Our work thus confirms the prior assignment of the AC of **1**.

(51) Ruud, K.; Taylor, P. R.; Åstrand, P.-O. *Chem. Phys. Lett.* **2001**, *337*, 217.

The most important outcome of this work is the demonstration of the utility of state-of-the-art DFT calculations of transparent spectral region specific rotations for the assignment of the AC's of chiral alkanes. For molecules whose [α] values are significantly greater than the error level of the calculational methodology, calculation of [α] values provides a straightforward method for the assignment of their AC's. In the present study, we have firmly established the AC of PHTP to be *S*(+)/*R*(−), the AC arrived at earlier, but by methods whose reliability was questionable. In future studies we plan to report on the AC's of a much wider range of chiral alkanes.

At the same time, we have demonstrated that the assignment of the AC's of chiral alkanes is unreliable for molecules whose [α] values are comparable to or smaller than the error level of the calculational methodology. We have anticipated this outcome in a prior study of the accuracy of DFT $[\alpha]_D$ calculations,[2b] but we have not previously documented specific cases where calculated and experimental $[\alpha]_D$ values differ in sign. Our work here provides the first examples, specifically for *trans*-pinane and *endo*-isocamphane. Since the AC's of these molecules are incontrovertible, we can exclude the possibility of erroneous AC's for these molecules as an explanation for the discrepancy in the signs of $[\alpha]_D$ values. There is no reason to believe that this conclusion is specific to alkanes, and we expect to encounter further examples of such incorrect sign predictions of small $[\alpha]_D$ values for molecules containing a wider range of functional groups in future studies of other classes of organic molecule.

In this work the molecules studied have been limited to conformationally rigid alkanes. In the case of conformationally flexible alkanes, where more than one conformation is significantly populated at room temperature, the predicted rotation is the population-weighted average of the rotations of individual conformations:

$$[\alpha]_\nu = \sum_i x_i [\alpha]_\nu^i$$

where x_i is the fractional population of conformer i, whose specific rotation is $[\alpha]_\nu^i$. The accuracy of predicted rotations is then determined not only by the accuracy of calculated $[\alpha]_\nu^i$ values, but also by the accuracy of the populations x_i. These can be obtained either experimentally or theoretically. In either case, uncertainties will exist in x_i values, leading to uncertainties in calculated $[\alpha]_\nu$ values. When all conformers exhibit $[\alpha]_\nu^i$ of the same sign, the sign of $[\alpha]_\nu$ is independent of the x_i values. However, when, as is often the case, different conformations exhibit $[\alpha]_\nu^i$ values of varying sign, the sign of the predicted $[\alpha]_\nu$ can be dependent on the x_i values, and sensitive to errors in these latter. We have discussed this issue in detail previously.[4b] The bottom line is that the accuracies of predicted [α] values in flexible molecules are always lower than those for rigid molecules and the lowering of accuracy can be substantial when the significantly populated conformations exhibit [α] values of varying sign. This must be taken into account in assigning AC's for conformationally flexible chiral alkanes.

To date, the applications of TDDFT optical rotation calculations to the determination of AC's for molecules whose AC's were not previously assigned are limited in number.[4] In almost all cases, experimental $[\alpha]_D$ values were >50. However, in the cases of *o*-Br-phenylglycidic acid methyl ester, **24**, $[\alpha]_D$ +23 (CCl_4),[4b] and *tert*-butyl-1-(2-methylnaphthyl)phosphine oxide, **25**, $[\alpha]_D$ −18.1/+16.4 (CH_2Cl_2),[4f] this was not so. Given also the conformational flexibility of **24**[4b] and **25**[4f] our results here show that the predictions of TDDFT optical rotation calculations cannot be assumed to predict the sign of $[\alpha]_D$ with certainty. Fortunately, for both of these molecules VCD experiments have defined the AC's unambiguously and shown that the AC's arrived at from $[\alpha]_D$ are in fact correct. We note also the case of CHFClBr, **26**, whose $[\alpha]_D$ is extremely small: 1.6 (neat)/1.8 (cyclohexane). Polavarapu[4e] has reported TDDFT optical rotation calculations for **26** and claimed verification of the preestablished AC of **26** from the agreement in sign of calculated and experimental $[\alpha]_D$ values. Our results here demonstrate that, to the contrary, the optical rotation calculations for **26** are far from the accuracy required to enable the AC of **26** to be reliably deduced.

Prior to the development of TDDFT methods for calculating $[\alpha]_D$ values, Hartree−Fock (HF) methods were used to assign the AC's of several molecules.[52] The HF method predicts $[\alpha]_D$ values of substantially lower accuracy than the DFT method (using hybrid functionals). For a set of 28 molecules studied earlier the average deviation of HF/aug-cc-pVDZ $[\alpha]_D$ values from experiment was 62.7.[2b] In addition, earlier HF calculations used very small basis sets such as 6-31G, 6-31G*, 6-31G**, and DZP. With such small basis sets, the accuracy of $[\alpha]_D$ values is further degraded. For the 28 molecule set, HF 6-31G* and DZP calculations gave average deviations of 69.4 and 77.2, respectively.[2b] Thus, reliable AC's can only be established on the basis of HF calculations with small basis sets for rigid molecules with very large $[\alpha]_D$ values, and certainly ≫30. For conformationally flexible molecules, the threshold is even greater. Unfortunately, in most of the cases where AC's were assigned using HF calculations, $[\alpha]_D$ values were quite small and in addition, with one exception, the molecules studied were conformationally flexible. The indolone 1,3,5,6-tetramethyl-1,3-dihydroindol-2-one, **27**, the sole rigid molecule, has $[\alpha]_D$ −15.6 ($CHCl_3$).[52a] The highly flexible natural products plakortolide G, **28** and pitiamide A, **29**, have $[\alpha]_D$ +6.0 ($CHCl_3$)[52a] and −10.3 ($CHCl_3$)[52c] respectively. The accuracies of the HF calculations are certainly insufficient to reliably assign the AC's of these molecules, and the latter are accordingly at this time undefined.

Acknowledgment. We are grateful to NSF for a grant to P.J.S. (grant CHE-0209957), to the USC Center for High Performance Computing for computer time, and to Dr. F. J. Devlin for advice and assistance.

Supporting Information Available: Cartesian coordinates of B3LYP/6-31G* optimized geometries of molecules **1**−**23**; potential energy surface scans for molecules **16** and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO048571N

(52) (a) Kondru, R. K.; Chen, C. H.-T.; Curran, D. P.; Beratan, D. N.; Wipf, P. *Tetrahedron*: *Asymmetry* **1999**, *10*, 4143. (b) Kondru, R. K.; Wipf, P.; Beratan, D. N. *J. Phys. Chem. A* **1999**, *103*, 6603. (c) Ribe, S.; Kondru, R. K.; Beratan, D. N.; Wipf, P. *J. Am. Chem. Soc.* **2000**, *122*, 4608. (d) Perry, T. L.; Dickerson, A.; Khan, A. A.; Kondru, R. K.; Beratan, D. N.; Wipf, P.; Kelly, M.; Hamann, M. T. *Tetrahedron* **2001**, *57*, 1483.