JOC*Note*

Absolute Configuration of *tert*-Butyl-1-(2-methylnaphthyl)phosphine Oxide

Feng Wang, Yan Wang, Prasad L. Polavarapu,*
Tingyu Li, Józef Drabowicz,†
K. Michal Pietrusiewicz,‡,§ and Krystyna Zygo§

Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37235, Center of Molecular and Macromolecular Studies, Polish Academy of Sciences, 93-236 Łódź, Sienkiewicza 112, Poland, Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw, Poland, and Department of Organic Chemistry, Maria Curie-Skłodowska University, Lublin, Poland

prasad.l.polavarapu@vanderbilt.edu

Received May 6, 2002

Abstract: The enantiomers of *tert*-butyl-1-(2-methylnaphthyl)phosphine oxide **1** have been separated using a homemade HPLC column and an analytical gradient system. Vibrational absorption and circular dichroism spectra for both enantiomers have been measured in CD_2Cl_2 and CH_2Cl_2 solutions in the 2000−900 cm^{-1} region. The fully relaxed potential energy surface of (*S*)-*tert*-butyl-1-(2-methylnaphthyl)phosphine oxide, obtained using the B3LYP functional with a 6-31G* basis set, indicated two stable conformers with their populations in a ∼2:1 ratio. The vibrational absorption and VCD spectra are predicted for these two conformers using the B3LYP functional with a 6-31G* basis set. The comparison of predicted and experimental spectra indicated that (+)-*tert*-butyl-1-(2-methylnaphthyl)phosphine oxide is in the (*S*)-configuration. This assignment is supported by the ab initio prediction of positive optical rotation for the most stable conformer with an (*S*)-configuration and the nonequivalence sense of the *tert*-butyl group chemical shift observed in the ^1H NMR spectrum of this enantiomer measured in the presence of (+)-(*S*)-mandelic acid as a chiral solvating agent.

The determination of absolute configuration using electronic circular dichroism (ECD)[1] or molecular optical rotations[2] requires either reliable quantum mechanical predictions of these chiroptical properties or establishment of reliable empirical rules relating these properties to the absolute configuration. The prediction of ECD requires a reliable description of the excited electronic states[3] and that of optical rotation requires establishing the reliability of predictions[4] for phosphorus-containing compounds. Reliable empirical rules establishing the connection between absolute configuration and ECD/optical rotation for chiral phosphorus compounds do not exist at the present time. The absolute configuration can sometimes be determined by the steric course of the reactions involved in the synthesis of a given chiral compound. However, this procedure is not applicable if the enantiomers are separated from the racemic compound using a chiral column. The fact that the absolute configuration of *tert*-butyl-1-(2-methylnaphthyl) phosphine oxide **1** remains unknown, despite the study[5] of its ECD spectra, supports the above-mentioned statements. Nevertheless, the conformations of **1** have been studied using NMR spectroscopy,[5] and the presence of two stable conformations at ambient temperature was suggested.

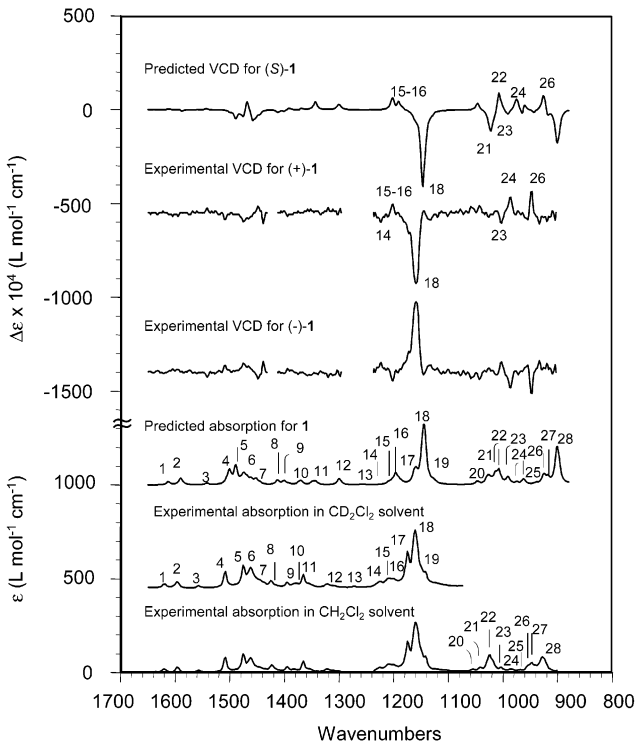
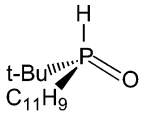


FIGURE 1. The absorption (bottom three traces) and VCD (top three traces) spectra of enantiomeric **1**.



(*S*)-**1**

Vibrational circular dichroism (VCD)[6] is an independent spectroscopic method to determine the absolute

* To whom correspondence should be addressed. Fax: (615) 322-4936.

† Center of Molecular and Macromolecular Studies, Polish Academy of Sciences.

‡ Institute of Organic Chemistry, Polish Academy of Sciences.

§ Maria Curie-Skłodowska University.

(1) Nakanishi, K.; Berova, N.; Woody, R. W. *Circular dichroism: Principles and Applications*; VCH Publishers: New York, 1994.

(2) Polavarapu, P. L. *Mol. Phys.* **1997**, *91*, 551.

(3) Furche, F., Ahlrichs, R., Wachsmann, C., Weber, E., Sobanski, A., Vogtle, F., Grimme, S. *J. Am. Chem. Soc.* **2000**, *122*, 1717.

(4) Stephens, P. J.; Devlin, F. J.; Cheeseman, J. R.; Frisch, M. J. *J. Phys. Chem. A* **2001**, *105*, 5356.

(5) Gasparrini, F.; Lunazzi, L.; Mazzanti, A.; Pierini, M.; Pietrusiewicz, K. M.; Villani, C. *J. Am. Chem. Soc.* **2000**, *122*, 4776.

(6) (a) Stephens, P. J.; Lowe, M. A. *Annu. Rev. Phys. Chem.* **1985**, *36*, 213. (b) Nafie, L. A. *Annu. Rev. Phys. Chem.* **1997**, *48*, 357. (c). Dukor, R. K.; Keiderling. T. A.; Gut, V. *Int. J. Pep. Prot. Res.* **1991**, **38**, 198. (d). Polavarapu, P. L. *Vibrational Spectra: Principles and applications with emphasis on optical activity*; Elsevier: New York, 1998.

10.1021/jo025908h CCC: $22.00
Published on Web 08/03/2002

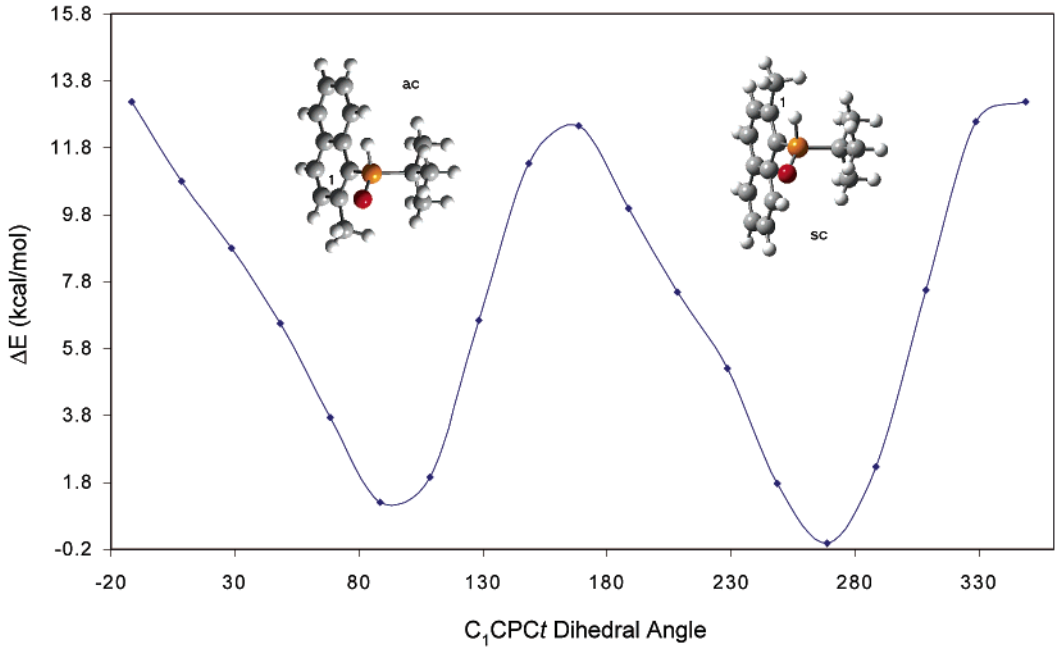


FIGURE 2. Fully relaxed B3LYP/6-31G* energy of (*S*)-*tert*-butyl-1-(2 methylnaphthyl)phosphine oxide as a function of the C_1-CPC*t* dihedral angle where C*t* is the central carbon atom of *text*-butyl group. The conformations **sc** and **ac** are the structures that correspond to the two potential energy minima (see Table 1).

TABLE 1. Conformations and Energies of (*S*)-*tert*-Butyl-1-(2-methylnaphthyl)phosphine Oxide[a]

	converged[b]			energy[c]			
conformer	C_1CPC*t*	C_1CPO	C_1CPH	electronic	Gibbs	ΔE[d] (kcal)	pop[e] (%)
sc	−91.5	139.1	14.7	−999.647152	−999.386631	0.000	67.5
ac	97.1	−31.9	−155.4	−999.645411	−999.385943	0.432	32.5

[a] See Figure 2 for the labels. [b] Dihedral angles in degrees. [c] In hartrees. [d] Relative energy difference, in kcal/mol. [e] Percent population based on Gibbs energies.

configuration and predominant conformations in the solution phase. The availability of quantum mechanical programs[7] that provide reliable predictions of VCD using density functional theory,[8] and of commercial VCD instruments, facilitated the predictions of absolute configurations using VCD. Numerous examples are now available where VCD has been successfully used in confirming the known absolute configurations, in either resolving the ambiguous literature assignments or unambiguous determination of absolute configuration, in addition to determining the predominant conformations in the solution phase.[9] The purpose of this work is to report the absolute configuration of **1** using the experimental, and state-of-the-art quantum mechanical predictions of, VCD spectra for the enantiomers of **1**.

The VCD spectra in CH_2Cl_2 solution and absorption spectra in both CH_2Cl_2 and CD_2Cl_2 solutions (after subtracting the solvent spectra) are shown in Figure 1. The 1412−1432 and 1237−1297 cm^{-1} regions in VCD spectra, where CH_2Cl_2 solvent absorption interfered, are not shown. Similarly, the region below ~1100 cm^{-1} is not shown for the spectra in CD_2Cl_2 solvent due to interference from solvent absorption. For theoretical predictions, the fully relaxed potential energy surface of (*S*)-*tert*-butyl-1-(2-methylnaphthyl)phosphine oxide was scanned by varying the dihedral angle of C_1CPC*t* and using the B3LYP functional with 6-31G* basis set. Two global minima and maxima were found (Figure 2). The two minima correspond to synclinal **sc** (P−H hydrogen close to 2-methyl substituent) and anticlinal **ac** conformations and the maxima lie 12.5 and 13.2 kcal/mol higher in

(7) *7.*Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*; Gaussian, Inc.: Pittsburgh, PA, 1998.

(8) Cheeseman, J. R.; Frisch, M. J.; Devlin, F. J.; Stephens, P. J. *Chem. Phys. Lett.* **1996**, *252*, 211.

(9) (a)Wang, F.; Wang, H.; Polavarapu, P. L.; Rizzo, C. J. *J. Org. Chem.* **2001**, *66*, 3507. (b)Wang, F.; Polavarapu, P. L.; Drabowicz, J.; Mikołajczyk, M. *J. Org. Chem.* **2000**, *65*, 7561;(c). Wang, F.; Polavarapu, P. L.; Drabowicz, J.; Mikołajczyk, M.; Łyżwa, P. *J. Org. Chem.* **2001**, *66*, 9015. (d). Stephens, P. J.; Aamouche, A.; Devlin, F. J.; Superchi, S.; Donnoli, M. I.; Rosini, C. *J. Org. Chem.* **2001**, *66*, 3671. (e). Dyatkin, A. B.; Freedman, T. B.; Cao, X.; Dukor, R. K.; Maryanoff, B. E.; Maryanoff, C. A.; Mathhews, J. M.; Shaw, R. D.; Nafie, L. A. *Chirality* **2002**, *14*, 215. (f). Stephens, P. J.; Devlin, F. J.; Aamouche, A. *J. Am. Chem. Soc.* **2000**, *122*, 2346. (g). Devlin, F. J.; Stephens, P. J.; Scafato, P.; Superchi, S.; Rosini, C. *Tetrhedron*: *Asymmetry* **2001**,*12*, 1551. (h). Wang, F.; Polavarapu, P. L. *J. Phys. Chem. A.* **2001**, 105, 6991. (i). Wang, F.; Polavarapu, P. L. *J. Phys. Chem. A.* **2000**, *104*, 10683.

energy above that of **sc** conformation. On the basis of the Gibbs energies, the populations of **sc** and **ac** conformers are predicted to be 67% and 33%, respectively, for isolated molecule (Table 1). The absorption and VCD intensities were calculated for **sc** and **ac** conformations at the B3LYP/6-31G* level. The population-weighted theoretical spectra are compared to the experimental spectra in Figure 1. The absorption bands in the population weighted predicted spectrum show one-to-one correspondence with the absorption bands in experimental spectrum. Two notable differences are observed: (a) The two bands (4, 5) around 1500 cm^{-1} are closer to each other in the predicted spectrum than those shown in the experimental spectra. (b) The band (28) at ~920 cm^{-1} is relatively higher in intensity than the corresponding band in experimental spectrum. Except for these differences, the experimental spectra are considered to be in agreement with the predicted absorption spectrum.

The predicted population-weighted VCD spectrum is in excellent agreement with the experimental VCD spectrum. A significant negative VCD band (18) around 1160 cm^{-1} is present in the predicted spectrum for (*S*)-**1**. The experimental VCD spectrum of (+)-**1** shows the same negative VCD band, while that of (−)-**1** shows the positive VCD band. Thus, (+)-*tert*-butyl-1-(2-methylnaphthyl)-phosphine oxide is assigned the (*S*)-configuration.

This assignment is supported by two other investigations: (a) ab initio predictions of optical rotation[10] using density functional theory that indicated[11] positive optical rotation for **sc** conformer with the (*S*)-configuration, and (b) the analysis of the ^1H NMR spectra of diastereomeric complexes of the enantiomers of **1** and of *tert*-butylphenylphosphine oxide with (+)-(*S*)-mandelic acid.[12] If one assumes that the nonequivalence sense for the *tert*-butyl group chemical shifts in the ^1H NMR spectra of the complexes of a family of the *tert*-butylarylphosphine oxides with the given enantiomer of mandelic acid should remain the same within the family, then the low nonequivalence sense observed in the spectrum of (+)-**1** and the high nonequivalence sense observed in the spectrum of (+)-(*R*)-*tert*-butylphenylphosphine oxide can be considered as an independent evidence that (+)-*tert*-butyl-1-(2-methylnaphthyl)phosphine oxide is of the (*S*)-configuration.[12]

Experimental Section

Synthesis. The racemic **1** was prepared as described in ref 5 by the condensation of 1-(2-methylnaphthyl)magnesium bromide with *tert*-butyldichlorophosphine and quenching the formed product, *tert*-butyl-1-(2-methylnaphthyl)chlorophosphine, in situ with 25% sulfuric acid. The enantiomers of **1** were separated from the racemic sample (80 mg of racemic sample was dissolved in 200 μL of methylene chloride) on a homemade chiral HPLC column.[13] The sample solution was injected into the column (20 μL for each injection with 30% heptane in methylene chloride as eluting solvent and detected at 238 nm). The $[\alpha]_D$ measured in CH_2Cl_2 for the first and second eluted enantiomers are −18.1 and +16.4, respectively.

Measurements. The infrared and VCD spectra were recorded on a commercial Fourier transform VCD spectrometer.[9a] The VCD spectra for both enantiomers of *tert*-butyl-1-(2-methylnaphthyl)phosphine oxide were obtained both in CD_2Cl_2 and CH_2Cl_2 solutions with 1 h data collection time at 4 cm^{-1} resolution in the 2000−900 cm^{-1} region. For (+)-**1**, spectra were measured at ~0.162 M. For (−)-**1**, spectra were measured at ~0.122 M. In the presented absorption spectra, the solvent absorption was subtracted out. In the presented VCD spectra, the raw VCD spectrum of the solvent was subtracted.

Calculations. The fully relaxed potential energy surface, ab initio vibrational frequencies, absorption, and VCD intensities for (*S*)-**1** were calculated using the Gaussian 98 program.[7] The calculations used the density functional theory with the B3LYP functional and 6-31G* basis set. The procedure for calculating the VCD intensities using DFT theory is due to Cheeseman et al.[8] as implemented in the Gaussian 98 program. The theoretical absorption and VCD spectra were simulated with Lorentzian band shapes and 5 cm^{-1} full width at half-height. Since the ab initio predicted band positions are higher than the experimental values, the ab initio frequencies were scaled with 0.96. The optical rotations were calculated using a developmental version of the DALTON program.[10]

Acknowledgment. Grants from NSF (CHE0092922 to P.L.P.), NIH (GM 63812 to T.L.) and Vanderbilt University are gratefully acknowledged. Studies in Łódź were partially supported by the State Committee for Scientific Research (KBN Grant 4TO9A 105 22 to J.D.. We thank Dr. Kenneth Ruud for the developmental version of the Dalton program used in the optical rotation calculations.

Supporting Information Available: Predicted absorption and VCD spectra for two conformers of (*S*)-*tert*-butyl-1-(2-methylnaphthyl)phosphine oxide **1**; experimental VCD spectra of **1** in CD_2Cl_2 solvent; table with vibrational band positions and assignments; and Cartesian coordinates for the two conformations of (*S*)-**1**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO025908H

(10) Helgaker, T.; Jensen, H. J. A.; Joergensen, P.; Olsen, J.; Ruud, K.; Aagren, H.; Auer, A. A.; Bak, K. L.; Bakken, V.; Christiansen, O.; Coriani, S.; Dahle, P.; Dalskov, E. K.; Enevoldsen, T.; Fernandez, B.; Haettig, C.; Hald, K.; Halkier, A.; Heiberg, H.; Hettema, H.; Jonsson, D.; Kirpekar, S.; Kobayashi, R.; Koch, H.; Mikkelsen, K. V.; Norman, P.; Packer, M. J.; Pedersen, T. B.; Ruden, T. A.; Sanchez, A.; Saue, T.; Sauer, S. P. A.; Schimmelpfennig, B.; Sylvester-Hvid, K. O.; Taylor, P. R.; Vahtras, O. Dalton, a molecular electronic structure program, Release 1.2, 2001.

(11) Specific rotations predicted using B3LYP functional and 6-31G* basis set using DALTON program[10] gave +132 for (*S*)-**sc** and −71 for (*S*)-**ac** conformers. Ab initio optical rotation predictions were also verified for *tert*-butylphenylphosphine oxide and *tert*-butylphenylthiophosphinic acid for consistency.

(12) The *tert*-butyl signal for (+)-1-(2-methylnaphthyl)phosphine oxide **1** was at lower field than that for the (−)-enantiomer by about 1.6 Hz in the presence of (+)-(*S*)-mandelic acid. The *tert*-butyl signal for (+)-(*R*)-*tert*-butylphenylphosphine oxide was at higher field than that for the (−)-(*S*) enantiomer by about 1.4 Hz in the presence of an equivalent amount of (+)-(*S*)-mandelic acid.

(13) The HPLC column is made up of a Dnb-D-Asn-Thr-Aun-NH-$(CH_2)_3$silica stationary phase where aminoundecanoic (Aun) acid served as the linker and dinitrobenzoyl(Dnb)-D-asparagine(Asn)-L-threonine-(Thr) served as the peptide selector.