also: b) R. Mahrwald, *Chem. Rev.* **1999**, 1095; c) T. D. Machajewski, C.-H. Wong, *Angew. Chem.* **2000**, *112*, 1406; *Angew. Chem. Int. Ed.* **2000**, *39*, 1352.

[10] For a synthesis that leads to products with low *ee* values, see: C. M. Gasparski, M. J. Miller, *Tetrahedron* **1991**, *47*, 5367.

[11] For a Mukaiyama-type reaction with ketene silyl acetal of glycine Schiff base, see: M. Horikawa, J. Busch-Petersen, E. J. Corey, *Tetrahedron Lett.* **1999**, *40*, 3843.

[12] a) A. Saeed, D. W. Young, *Tetrahedron* **1992**, *48*, 2507; b) V. P. Vassilev, T. Uchiyama, T. Kajimoto, C.-H. Wong, *Tetrahedron Lett.* **1995**, *36*, 5063; c) T. Kimura, V. P. Vassilev, G.-J. Shen, C.-H. Wong, *J. Am. Chem. Soc.* **1997**, *119*, 11734; d) T. Miura, M. Fujii, K. Shingu, I. Koshimizu, J. Naganoma, T. Kajimoto, Y. Ida, *Tetrahedron Lett.* **1998**, *39*, 7313; e) N. Wymer, E. J. Toone, *Curr. Opin. Chem. Biol.* **2000**, *4*, 110; f) B. G. Jackson, S. W. Pedersen, J. W. Fisher, J. W. Misner, J. P. Gardner, M. A. Staszak, C. Doecke, J. Rizzo, J. Aikins, E. Farkas, K. L. Trinkle, J. Vicenzi, M. Reinhard, E. P. Kroeff, C. A. Higginbotham, R. J. Gazak, T. Y. Zhang, *Tetrahedron* **2000**, *56*, 5667.

[13] For reviews on the use of glycine Schiff base for the preparation of enantiomerically pure α-amino acids, see: a) T. Abellan, R. Chinchilla, N. Galindo, G. Guillena, C. Najera, J. M. Sansano, *Eur. J. Org. Chem.* **2000**, 2689; b) M. J. O'Donnell, *Aldrichimica Acta* **2001**, *34*, 3.

[14] a) T. Ooi, M. Kameda, K. Maruoka, *J. Am. Chem. Soc.* **1999**, *121*, 6519; b) T. Ooi, M. Takeuchi, M. Kameda, K. Maruoka, *J. Am. Chem. Soc.* **2000**, *122*, 5228; c) T. Ooi, M. Kameda, H. Tannai, K. Maruoka, *Tetrahedron Lett.* **2000**, *41*, 8339; d) T. Ooi, K. Doda, K. Maruoka, *Org. Lett.* **2001**, *3*, 1273; e) T. Ooi, M. Takeuchi, K. Maruoka, *Synthesis* **2001**, 1716.

[15] Attempted reaction of **2** with 3-phenylpropanal using *O*-allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide as catalyst under otherwise similar conditions gave rise to **3** ($R = PhCH_2CH_2$) in 60% yield with an *anti*/*syn* ratio of 1:5.3; the enantiomeric excess of the major *syn* isomer was 25%. Similar *syn* selectivity was observed in the Mukaiyama-type reaction catalyzed by the cinchonidine-derived bifluoride salt.[11]

[16] M. M. Palian, R. Polt, *J. Org. Chem.* **2001**, *66*, 7178.

[17] Treatment of the aldol product *anti*-**3** ($R = CH_3$) with HCl (6 N) in MeOH gave rise to the corresponding β-hydroxy-α-amino acid hydrochloride; its absolute configuration was determined to be 2*S*,3*S* by comparison of the optical rotation value with that of the hydrochloride salt of commercially available L-*allo*-threonine.

The Absolute Configuration of Bromochlorofluoromethane**

Prasad L. Polavarapu*

Bromochlorofluoromethane is the simplest chiral molecule that is used as an example to illustrate chirality or asymmetric carbon atoms, yet its absolute configuration remains uncertain. The synthesis of bromochlorofluoromethane in a pure form was achieved by Berry and Sturtevant in 1942.[1] They determined its boiling point, melting point, and refractive dispersion, but the individual enantiomers were not resolved. Despite the unavailability of enantiomers and their optical rotation values, Brewster hypothesized that (*S*)-bromochlorofluoromethane would have positive optical rotation, assuming that the polarizabilities decrease in the order Br > Cl > H > F.[2] Hargreaves and Modarai were able to resolve the enantiomers of 1-bromo-1-chloro-1-fluoroacetone and convert them into the corresponding bromochlorofluoromethane enantiomers.[3] They reported the specific rotations to be +0.20 and −0.13. In 1973 Applequist predicted, using an atom–dipole interaction model and assuming the polarizabilities to be in the order, Br > Cl > F > H, that (*S*)-bromochlorofluoromethane would have positive optical rotation.[4] However, the different polarizability orders chosen by Brewster and Applequist would yield opposite conclusions.[5] Collet and co-workers achieved optical resolution of bromochlorofluoromethane by enantioselective inclusion in cryptophan C.[6] Using the NMR resonance signals of (+) and (−) enantiomers encapsulated in cryptophan, they estimated the enantiomeric excess and maximum rotation values at five different wavelengths. In a different approach, Wilen et al. also resolved the enantiomers of bromochlorofluoromethane using brucine[5] and addressed the ambiguity remaining in the absolute configuration of bromochlorofluoromethane; Brewster and Applequist had arrived at the same assignment but using mutually conflicting polarizability trends. Wilen et al. concluded that "experimental determination of the absolute configuration of bromochlorofluoromethane is a challenge".[5] Using a quantum-mechanical static method, the specific rotation of (*R*)-bromochlorofluoromethane at the sodium D line was predicted (without the Lorentz factor) to be −6.[7,8] Comparison of this value with the experimental value of −1.78 reported by Collet et al. for enantiopure (−)-bromochlorofluoromethane, and based on the comparison of experimental and ab initio predicted Raman optical-activity (ROA) spectra, it was concluded that the absolute configuration of bromochlorofluoromethane is (*S*)-(+) and (*R*)-(−).[7]

Previous conclusions[7] on the absolute configuration were based on quantum-mechanical calculations of both ROA and specific rotation, carried out at the Hartree–Fock (HF) level using smaller basis sets. Since then, evidence has been collected[9] to indicate that the HF level calculations, because of lack of electron correlation, are not quantitatively accurate. DFT,[10] which includes electron correlation using density functionals, has now been widely accepted as the preferred approach for predicting molecular properties accurately. For reliable quantum mechanical predictions of specific rotations, those predicted at the HF level using small basis sets are not considered to be adequate and predictions with DFT and larger basis sets are necessary. Electron correlation and larger basis sets are also important for molecular polarizability derivatives, and hence Raman properties. Because the absolute configuration of bromochlorofluoromethane was suggested[7] based on HF calculations, the previously predicted specific rotation and ROA parameters of bromochlorofluoromethane must be verified using DFT and larger basis sets. The DFT method has been implemented recently for the prediction of specific rotation[11a] and of ROA[11b] in the quantum-mechanical program DALTON.[12] Thus it is important to reinvestigate the specific rotation and ROA of bromochlorofluoromethane. Recently Grimme[13] has reported DFT predictions of $[\alpha]_D$ for bromochlorofluoromethane. Because

---

[*] Prof. Dr. P. L. Polavarapu
Department of Chemistry
Vanderbilt University
Nashville, TN 37235 (USA)
Fax: (+1) 615-322-4936
E-mail: prasad.l.polavarapu@vanderbilt.edu

[**] I thank NSF (CHE0092922) for research grants and Dr. K. Ruud for the developmental version of DALTON program which was used for the calculations reported here.

those calculations were origin-dependent, the predicted rotations with a larger aug-SV(d) basis set for the *S* enantiomer varied from 1.0–5.3, depending on the choice of origin. More recently, Autschbach et al. reported $[\alpha]_D$ predictions for (*S*)-bromochlorofluoromethane using various nonhybrid density functionals.[14] Their predictions for $[\alpha]_D$ varied from 1.3–4.0 depending on the functional used. These two calculations, although they supported the previous assignment of absolute configuration,[7] did not investigate the optical rotatory dispersion in bromochlorofluoromethane, which has been experimentally measured.[6,7]

Herein we report a) the origin-independent DFT predictions of specific rotation as well as its wavelength dependence and b) DFT predictions of ROA parameters for (*S*)-bromochlorofluoromethane, both using very large basis sets. A comparison between these predictions with the corresponding experimental values provides state-of-the-art conclusions on the absolute configuration of bromochlorofluoromethane.

Specific rotation was computed using the DALTON program.[12] A linear response method and gauge including atomic orbitals were used. The Lorentz factor, $(n^2+2)/3$ where n is the refractive index, which was included in earlier calculations[7,8] was not included in the present calculations. Specific rotations were calculated at five different wavelengths. For comparison, calculations were also carried out at both HF and B3LYP levels of theory. Five different sets of specific rotations calculations were undertaken using the geometry optimizations and levels of theory described in Table 1. Unlike in the previous studies,[7,13,14] it is possible here to verify the trend in dispersion of specific rotation with wavelength, in addition to verifying the sign and magnitude of specific rotation.

A number of observations can be made from the specific rotation values compiled in Table 1: a) The HF/DZP values represent the lowest level predictions of all those reported in Table 1, yet they give the same sign and similar dispersion trend as those obtained in the highest level calculation. The magnitudes of HF/DZP-predicted specific rotations however differ significantly from those observed; b) the rotatory dispersion predicted in B3LYP/6–311++G(2d,2p) calculations at MP2/DZP geometry does not have the same trend as that observed in the experimental values, but that predicted at B3LYP/6–311++G(2d,2p) geometry has the same trend as that of the experimental values. As the differences in these two geometries are minor (see Table 1), these differences in the dispersion trend probably arise because contributions from either Rydberg orbitals or valence orbitals (or both) are not properly accounted for in the B3LYP/6–311++G(2d,2p) calculation at the MP2/DZP geometry. These observations suggest that it is preferable, at least for bromochlorofluoromethane, to calculate both the optimum geometry and the specific rotation using the same basis set. For this reason, large basis-set calculations were performed at B3LYP/6–311++G(2d,2p), B3LYP/aug-cc-pVDZ, and B3LYP/aug-cc-pVTZ level (see Table 1) at their respective optimum geometries; c) among these values, those obtained in the B3LYP/aug-cc-pVTZ calculation at B3LYP/aug-cc-pVTZ geometry are the highest level predictions and the results obtained therein are expected to be the most reliable ones. The predicted values in this calculation suggest that (+)-bromochlorofluoromethane is in the *S* configuration, not only because the predicted values are in close agreement (both in sign and magnitude) with experimental values, but also the predicted rotatory dispersion trend matches that observed in the experimental values. The same conclusion can be reached from the predictions at the B3LYP/6–311++G(2d,2p) and B3LYP/aug-cc-pVDZ levels.

Some additional factors should however be noted. The experimental specific rotations were reported for the neat liquid and for cyclohexane solutions.[5–7] In liquid bromochlorofluoromethane, one can anticipate the presence of dipole–dipole and dispersion interactions, but it is not obvious how these interactions would influence the specific rotation. Inclusion of the Lorentz factor, which represents bulk-phase effects, would increase the predicted values by a factor of $(n^2+2)/3$, while the Cavity Field model of Applequist[15] would increase the predicted values by $(5n^2+1)/(4n^2+2)$. In either case the predicted sign of specific rotation would not be affected. First, because experimental rotations obtained for the neat liquid[6] and the cyclohexane solution[7] are the same within experimental error, it is probable that the solvent effect on specific rotations is insignificant and that bulk-phase effects would not have influenced the experimentally measured sign of specific rotation. Second, zero-point vibrational effects,[16] which are not included in the present calculations, are known to contribute to specific rotation. However they

Table 1. Experimental and predicted specific rotations for (*S*)-(+)-CHFClBr.

	DZP[a]		6-311++G(2d,2p)[a]		6-311++G(2d,2p)[b]		aug-cc-pVDZ[c]		aug-cc-pVTZ[d]		Experimental	
Wavelength [nm]	HF[e]	B3LYP[f]	HF[e]	B3LYP[f]	HF[e]	B3LYP[f]	HF[e]	B3LYP[f]	HF[e]	B3LYP[f]	Neat liquid[g]	(c = 6.5, cyclohexane)[h]
589	4.6	5.5	0.06	1.39	0.88	2.54	1.32	1.28	1.05	1.09	1.6	1.8
578	4.8	5.7	0.05	1.42	0.91	2.63	1.38	1.34	1.09	1.13	1.6	1.8
546	5.5	6.6	0.01	1.52	1.00	2.92	1.57	1.51	1.22	1.26	1.8	2.1
436	9.6	11.7	−0.39	1.6	1.39	4.28	2.68	2.51	1.89	1.85	2.7	3.2
365	15.6	19.6	−1.47	0.47	1.55	5.41	4.30	3.97	2.65	2.40	3.2	3.7

[a] The geometry used was optimized at the MP2 level with the DZP basis set. The lengths of the C−H, C−F, C−Cl, and C−Br bonds are respectively, 1.09, 1.3427, 1.758, and 1.9397 Å; the H-C-F, H-C-Cl, and H-C-Br angles are, respectively, 109.83, 108.86, and 107.06°. [b] The geometry used was optimized at the B3LYP level with the 6–311++G(2d,2p) basis set. The lengths of the C-H, C-F, C-Cl, and C-Br bonds are respectively, 1.0815, 1.3486, 1.7766, and 1.9611 Å; the H-C-F, H-C-Cl, and H-C-Br angles are, 109.96, 108.81, and 107.13°, respectively. [c] The geometry used was optimized at the B3LYP level with aug-cc-pVDZ basis set. The lengths of the C-H, C-F, C-Cl, and C-Br bonds are 1.0927, 1.3582, 1.7826, and 1.9571 Å, respectively; the H-C-F, H-C-Cl, and H-C-Br angles are 109.69, 108.76, and 107.78°, respectively.[d] The geometry used was optimized at the B3LYP level with the aug-cc-pVTZ basis set. The lengths of the C-H, C-F, C-Cl, and C-Br bonds are 1.0827, 1.3478, 1.7758, and 1.9559 Å, respectively; the H-C-F, H-C-Cl, and H-C-Br angles are 109.95, 108.66, and 107.28, respectively. [e] HF method. [f] Density-functional method with the B3LYP functional. [g] From reference [6].[h] The values given in reference [7] for the (−)-enantiomer were multiplied by −1 and scaled up to the pure enantiomer. c = concentration of solution.

Table 2. Experimental and predicted ROA properties of (*S*)-(+)-CHFClBr.

DZP		6-311 + + G(2d,2p)			aug-cc-pVDZ			aug-cc-pVTZ			Experimental[d]		Assignment[a]
HF[a]		B3LYP[b]		HF[c]	B3LYP[b]		HF[c]	B3LYP[b]		HF[c]			
Freq[e]	$\Delta_z \times 10^4$	Freq[e]	$\Delta_z \times 10^4$	$\Delta_z \times 10^4$	Freq[e]	$\Delta_z \times 10^4$	$\Delta_z \times 10^4$	Freq[e]	$\Delta_z \times 10^4$	$\Delta_z \times 10^4$	Freq[e]	$\Delta_z \times 10^4$	
3209	−0.2	3173	−0.3	−0.3	3162	−0.2	−0.2	3156	−0.2	−0.3	3022	−0.7	C−H stretch
1372	−0.5	1321	0.5	0.4	1293	1.0	1.1	1322	1.0	1.1	1305	−2.4	C−H bend
1266	0.0	1212	−1	0.03	1199	−3.0	−1.5	1215	−2.9	−1.6	1206	−2.8	C−H bend
1151	−0.3	1065	−0.2	−0.1	1057	0.3	0.1	1076	0.01	−0.01	1062	−4.5	C−F stretch
822	−3.9	744	−4.9	−2.0	750	−4.0	−1.6	743	−4.4	−1.8	774	−5.1	C−Cl stretch
678	3.8	634	3.2	1.7	641	2.4	1.3	639	2.4	1.3	662	5.9	C−Br stretch
439	0.6	417	1.1	1.2	415	1.6	1.5	418	1.2	1.3	427	10.2	inversion bend
321	0.3	305	0.01	−0.5	305	0.1	−0.4	306	0.2	−0.3	315	−2.1	C−halogen bend
233	−0.5	218	−0.3	−0.2	219	−0.3	−0.3	218	−0.4	−0.3	228	−1.9	C−halogen bend

[a] HF method with the DZP basis set. The geometry and force constants used were obtained at the MP2 level with the DZP basis set. These values are from reference [7]. [b] Density-functional method with the B3LYP functional. The geometry and force constants used were obtained at the same level using the basis set indicated. [c] HF method. The geometry and force constants used were obtained at the B3LYP level using the basis set indicated. [d] The experimental values given for the (−)-enantiomer in reference [7] are multiplied by −1. [e] Frequencies in cm^{-1}.

are not anticipated to be significant in bromochlorofluoromethane because the vibrations (except the C−H modes) involve heavy atoms and are of low frequency.

The same three large basis sets (6–311 + + G(2d,2p), aug-cc-pVDZ, and aug-cc-pVTZ) were used for ROA calculations. The optimum geometry and force constants were obtained at the DFT level with the B3LYP functional using the Gaussian 98 program.[17] These force constants were transferred to the ROA calculation and numerical differentiation of polarizability tensors was used, as implemented in the DALTON program. The density converged to 10^{-7} and the iterative solution of the linear-response equations to 5×10^{-5}. For comparison purposes, ROA calculations were also carried out at the HF level, using the same geometry and force constants obtained in the B3LYP calculation with each of three large basis sets. The depolarized circular-intensity differences (CIDs), Δ_z, predicted for (*S*)-bromochlorofluoromethane are summarized in Table 2 along with the experimental values for (+)-bromochlorofluoromethane and the values obtained in the previous study.[7] The following can be noted from these values: a) The ROA signs observed for six bands in the experimental spectrum at 3022 (C−H stretch), 1206 (C−H bend), 774 (C−Cl stretch), 662 (C−Br stretch), 427 (inversion bend at C atom), and 228 cm^{-1} (a C−halogen bend) have been reproduced (ignoring the cases in which the predicted magnitude is zero) in all of the calculations; b) the ROA sign of the band in the observed spectrum at 1305 cm^{-1} (another C−H bend) has not been reproduced in the calculations except for the HF calculation[7] with the DZP basis set; c) the ROA sign of the band observed at 1062 cm^{-1} (C−F stretch) has been reproduced in only four of the seven calculations, while that at 315 cm^{-1} (a halogen bend) has been reproduced in only three of the seven calculations; d) of the seven different calculations in Table 2, the experimentally observed ROA signs are reproduced for a minimum of six to a maximum of eight bands. This observation supports the conclusion reached earlier from specific rotations that (+)-bromochlorofluoromethane has the *S* configuration.

In summary, the highest theoretical level predictions of specific rotations and ROA parameters using 6–311 + + G(2d,2p), aug-cc-pVDZ, and aug-cc-PVTZ basis sets, in conjunction with the corresponding experimental data, reaffirm the assignment[7] of the absolute configuration of bromochlorofluoromethane to be (*S*)-(+) and (*R*)-(−).

Received: July 31, 2002 [Z19862]

---

[1] K. L. Berry, J. M. Sturtevant, *J. Am. Chem. Soc.* **1942**, *64*, 1599 – 1600.

[2] J. H. Brewster, *J. Am. Chem. Soc.* **1959**, 81, 5475 – 5483.

[3] M. K. Hargreaves, B. Modarai, *J. Chem. Soc. C*, **1971**, 1013 – 1025.

[4] J. Applequist, *J. Chem. Phys.* **1973**, *58*, 4251 – 4259.

[5] S. H. Wilen, K. A. Bunding, C. M. Kascheres, M. J. Weider, *J. Am. Chem. Soc.* **1985**, *107*, 6997 – 6998.

[6] J. Canceill, L. Lacombe, A. Collet, *J. Am. Chem. Soc.* **1985**, *107*, 6993 – 6996.

[7] J. Costante, L. Hecht, P. L. Polavarapu, A. Collet, L. D. Barron, *Angew. Chem.* **1997**, *109*, 917 – 919; *Angew. Chem. Int. Ed.* **1997**, *36*, 885 – 887.

[8] P. L. Polavarapu, *Mol. Phys.* **1997**, *91*, 551 – 554.

[9] J. R. Cheeseman, M. J. Frisch, F. J. Devlin, P. J. Stephens, *J. Phys. Chem. A.* **2000**, *104*, 1039 – 1046.

[10] R. G. Parr, W. Yang, *Density functional theory of atoms and molecules*, Oxford University, Oxford, **1989**.

[11] a) K. Ruud, T. Helgaker, *Chem. Phys. Lett.* **2002**, *352*, 533 – 539; b) K. Ruud, T. Helgaker, P. Bour, *J. Phys. Chem. A.* 2002, 106, 7448 – 7455.

[12] T. Helgaker, H. J. Aa. Jensen, P. Jørgensen, J. Olsen, K. Ruud, H. Ågren, A. A. Auer, K. L. Bak, V. Bakken, O. Christiansen, S. Coriani, P. Dahle, E. K. Dalskov, T. Enevoldsen, B. Fernandez, C. Hättig, K. Hald, A. Halkier, H. Heiberg, H. Hettema, D. Jonsson, S. Kirpekar, R. Kobayashi, H. Koch, K. V. Mikkelsen, P. Norman, M. J. Packer, T. B. Pedersen, T. A. Ruden, A. Sanchez, T. Saue, S. P. A. Sauer, B. Schimmelpfennig, K. O. Sylvester-Hvid, P. R. Taylor, O. Vahtras, *Dalton, a molecular electronic structure program*, Release 1.2 (**2001**). See dhttp://www.kjemi.uio.no/software/dalton/dalton.html.

[13] S. Grimme, *Chem. Phys. Lett.* **2001**, *339*, 380 – 388.

[14] J. Autschbach, S. Patchkovskii, T. Ziegler, S. J. A. van Gisbergen, E. J. Baerends, *J. Chem. Phys.* **2002**, *117*, 581 – 592.

[15] J. Applequist, *J. Phys. Chem.* **1990**, *94*, 6564 – 6573.

[16] K. Ruud, P. R. Taylor, P. Astrand, *Chem. Phys. Lett.* **2001**, *337*, 217 – 223.

[17] *Gaussian 98 Revision A.3*, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, J. A. Pople, Gaussian, Inc., Pittsburgh PA, **1998**.

0044-8249/02/4123-4546 $ 20.00+.50/0