J|A|C|S
COMMUNICATIONS

Pseudotetrahedral Polyhalocubanes: Synthesis, Structures, and Parity Violating Energy Differences

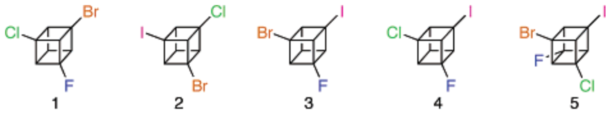
Andrey A. Fokin,[*,#,‡] Peter R. Schreiner,[*,#] Robert Berger,[§] Gregory H. Robinson,[‖]
Pingrong Wei,[‖] and Charles F. Campana[⊥]

*Institut für Organische Chemie der Justus-Liebig-Universität, Heinrich-Buff-Ring 58, 35392 Giessen, Germany,
Department of Organic Chemistry, Kiev Polytechnic Institute, pr. Pobedy, 37, 03056 Kiev, Ukraine, Frankfurt
Institute for Advanced Studies, J. W. Goethe University, Max-von-Laue-Str. 1, 60438 Frankfurt, Germany,
Department of Chemistry, University of Georgia, Athens, Georgia 30602-2556, and Advanced X-ray Solutions,
Bruker AXS Inc., Madison, Wisconsin 12345*

Received February 2, 2006; E-mail: andrey.fokin@org.chemie.uni-giessen.de; prs@org.chemie.uni-giessen.de

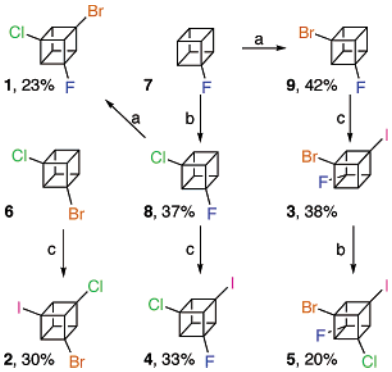
Polyhalomethanes have recently received increased attention as systems for potentially displaying measurable molecular parity violating effects, perhaps the most intriguing being the energy difference between the enantiomers of chiral compounds.[1,2] The parity violating energy difference (ΔE_{pv}) between the enantiomers of CHBrClF has been predicted to be on the order of 10^{-12} cm^{-1} *hc*, with the *S*-compound being more stable.[3] Estimates of the relative parity violating vibrational frequency difference $\Delta\nu/\nu$ between the C−F stretching fundamentals of (*R*)- and (*S*)-CHBrClF are on the order of 10^{-16}−10^{-17}, approximately four orders of magnitude smaller than the resolution achieved in recent high-resolution infrared studies of CHBrClF;[1] in CHBrFI, a relative shift of the C−F stretching fundamental of about 10^{-15} is expected.[4] One disadvantage of the chiral polyhalomethanes is their configurational instability.[5] Although we have recently shown that pseudotetrahedral adamantanes are accessible in high optical purity and are configurationally stable,[6] these compounds possess additional vibrational degrees of freedom that result in complex rovibrational spectra that make them less suitable for measuring parity violation effects. These effects are expected to be considerably smaller than those for the methane analogues. We now turn our attention to the smaller and far stiffer pseudotetrahedral polyhalocubanes (**1**−**5**), which probe the synthetic limits for halogenation reactions of strained hydrocarbons. We present herein the synthesis of all possible stable chiral pseudotetrahedral polyhalocubanes and estimate their parity violating energy differences together with selected parity violating vibrational frequency shifts.

Scheme 1. Chiral, Pseudotetrahedral Polyhalocubanes (Arbitrarily Depicted in Their *S*-Configurations)



We have recently demonstrated that our phase-transfer catalytic (PTC) halogenation protocol for aliphatic hydrocarbons[7,8] is similarly applicable to alkanes that contain highly strained three- and four-membered rings that normally undergo ring-opening reactions with halogen radicals,[9] especially in the case of cubane.[10] The PTC halogenations of monohalocubanes, involving highly selective $CHal_3$ radicals, lead mainly to *meta*-(1,3)-dihalocubanes; this selectivity is well understood.[8,11]

Scheme 2. Preparation of Polyhalocubanes (preparative yields)[a]



[a] Conditions: (a) *t*-BuOBr, CBr_4, CF_2Br_2, h·ν, 0 °C; (b) *t*-BuOCl, CCl_4, h·ν, 0 °C; (c) *n*-$C_6F_{13}I$, $Fe(AcAc)_2$, HOAc, $PhCO_4CPh$, 100 °C.

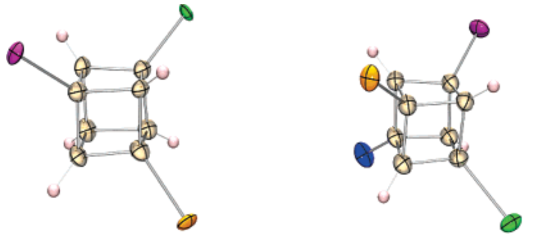
1-Bromo-3-chlorocubane (**6**) was prepared via PTC bromination of chlorocubane as described earlier; as dihalo- and fluorocubanes[12] react slowly with $^{\bullet}CHal_3$ radicals, we used more reactive radicals (*n*-$C_6F_{13}^{\bullet}$, *t*-BuO$^{\bullet}$) for the preparation of the polyhalocubanes (Scheme 2). The *ortho*- and *para*-positions in 1,3-dihalocubanes are deactivated toward radical attack, and the incorporation of a third halogen into the *meta*-position is more selective than for monohalocubanes. Accordingly, less selective radicals[13] give satisfactory *meta*-selectivities for the third halogenation. The iodination of 1,3-dihalocubanes **6**, **8**, and **9** following a modified Minisci protocol[14] gave **2**−**4**. Owing to the deactivation of the *ortho*-positions of 1,3,5-trihalocubanes, the chlorination with the normally unselective reagent *t*-BuOCl shows extraordinary high (ca. 95%) *meta*-selectivity for the preparation of **5**. The NMR spectra of (*R*/*S*)-**1** to (*R*/*S*)-**5** are in complete agreement with the substitution pattern (cf. Supporting Information (SI)); the crystal structures of (*R*/*S*)-**2** and (*R*/*S*)-**5** (Figure 1) confirm these findings. Owing to their near spherical shape, the GC or HPLC enantioseparation of **1**−**5** is currently not possible and will require even more powerful separation techniques than are available today.

We evaluated the parity violation energy differences for **1**−**5** and the vibrational frequency shifts for selected fundamentals utilizing a quasi-relativistic Hartree−Fock approach within the zeroth order regular approximation (HF-ZORA).[15] The parity violating potentials were computed with a modified version[15] of Turbomole,[16] whereas the "ordinary" parity conserving potentials and all equilibrium structures (at B3LYP/6-311G*/MIDI! for I) were computed with Gaussian (see SI);[17] for the parity violating potentials, V_{pv}, at the equilibrium geometries of (*S*)-**1**−**5**, see Table 1. Within the limits of a coordinate independent parity violating

---

[#] Justus-Liebig-Universität.
[‡] Kiev Polytechnic Institute.
[§] J. W. Goethe University.
[‖] University of Georgia.
[⊥] Bruker AXS Inc.

10.1021/ja060781p CCC: $33.50 © 2006 American Chemical Society



2 **5**

Figure 1. Molecular structures of **2** and **5** {50% probability ellipsoids for Br (orange), Cl (green), F (blue), I (purple), and C; *S*-enantiomers}. See Supporting Information for details of the X-ray structure analysis.

Table 1. Parity Violating Potential V_{pv} (in 10^{-15} cm^{-1} *hc*) at the Equilibrium Structure of the *S*-Enantiomer of **1**−**5** (cf. Scheme 1)

	1	**2**	**3**	**4**	**5**
V_{pv}	−22.8	−523.2	−644.2	−170.1	+100.8

potential and assuming an infinitely high barrier for stereomutation, ΔE_{pv} is to first order in Fermi's constant G_F given by $\Delta E_{pv} \approx 2V_{pv}$.

With the exception of **5**, the *S*-enantiomers are (within the above limits) predicted to be more stable than their mirror images. This parallels, remarkably, the results for the corresponding polyhalomethanes, of which also the *S*-enantiomers are computed to be more stable with the exception of CBrClFI.[18] Furthermore, the $|V_{pv}|$ ordering of **1**−**5** is **3** > **2** > **4** > **5** > **1** also is the same as that for the corresponding polyhalomethanes. The absolute values of the parity violating energy differences in the chiral polyhalocubanes are approximately one to two orders of magnitude smaller than those predicted for the related chiral polyhalomethanes. The largest absolute value for the parity violating energy difference is predicted for **3**, but this difference is expected to about a factor of two smaller than that in CHBrClF. Relative parity violating vibrational wavenumber splittings have been computed for **1** for selected fundamentals with C−F stretching participation and are predicted (see SI) to be on the order of -2×10^{-18} for ν_{11} and 3×10^{-19} for ν_{24}, with the latter being in the wavenumber range at which the CO_2 laser used in previous experiments operates. However, this is still two orders of magnitude smaller than that for CHBrClF. The fundamental of the mode dominated by the C−F stretching motion in **1** is shifted to wavenumbers well above 1300 cm^{-1} and is thus (in contrast to this mode in the halomethanes) presently not accessible with CO_2 lasers. Other fundamentals, overtones, and combination bands with larger splittings will be available, such as for **3**, suggesting chiral polyhalocubanes as promising candidates for future experiments regarding parity violation and as models for understanding molecular chirality.

There is no obvious relationship between the TD-B3LYP/6-311G* optical rotations $[\alpha]_D$ of **1**−**5** (+43.7, −70.2, −12.1, +31.7, +22.9° for the *S*-enantiomers, respectively) and those of the corresponding polyhalomethanes (−5.8, −15.2, +8.8, −4.6, +46.6°). However, the latter values are considerably off the experimental values for (*S*)-CHBrClF = −1.6°[5] and (*S*)-CHClFI = +2.5°.[19] A detailed discussion on the optical rotations of pseudotetrahedral polyhalo compounds will be forthcoming in a full account.

Acknowledgment. We thank Y. Okamoto for attempting the enantioseparation of **1**−**5**, J. Stohner as well as D. Luckhaus for discussions, and D. Pittman as well as B. C. Rinderspacher for the computed ORD data. This work was supported by the Deutsche Forschungsgemeinschaft and the Volkswagen Foundation. We thank the HLRN, HRZ Darmstadt and CSC Frankfurt for CPU time. P.R.S. and G.H.R. thank the National Science Foundation for support.

Supporting Information Available: NMR and X-ray data, experimental procedures, complete ref 17, *xyz* coordinates, and absolute energies for all species and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Ziskind, M.; Daussy, C.; Marrel, T.; Chardonnet, C. *Eur. Phys. J. D* **2002**, *20*, 219. (b) Daussy, C.; Marrel, T.; Amy-Klein, A.; Nguyen, C. T.; Borde, C. J.; Chardonnet, C. *Phys. Rev. Lett.* **1999**, *83*, 1554.
(2) (a) Quack, M.; Stohner, J. *Z. Phys. Chem.* **2000**, *214*, 675. (b) Quack, M.; Stohner, J. *Phys. Rev. Lett.* **2000**, *84*, 3807. (c) Viglione, R. G.; Zanasi, R.; Lazzeretti, P.; Ligabue, A. *Phys. Rev. A* **2000**, *62*, 052516. (d) Quack, M.; Stohner, J. *Chirality* **2001**, *13*, 745. (e) Quack, M.; Stohner, J. *J. Chem. Phys.* **2003**, *119*, 11228. (f) Crassous, J.; Monier, F.; Dutasta, J. P.; Ziskind, M.; Daussy, C.; Grain, C.; Chardonnet, C. *ChemPhysChem* **2003**, *4*, 541. (g) Crassous, J.; Chardonnet, C.; Saue, T.; Schwerdtfeger, P. *Org. Biomol. Chem.* **2005**, *3*, 2218. (h) Soulard, P.; Asselin, P.; Cuisset, A.; Moreno, J. R. A.; Huet, T. R.; Petitprez, D.; Demaison, J.; Freedman, T. B.; Cao, X.; Nafie, L. A.; Crassous, J. *Phys. Chem. Chem. Phys.* **2006**, *8*, 79.
(3) This is true for HF, CASSCF, MP2, and B3LYP, pure density functional methods favor the (*R*) configuration: (a) Schwerdtfeger, P.; Saue, T.; van Stralen, J. N. P.; Visscher, L. *Phys. Rev. A* **2005**, *71*, 012103. (b) Quack, M, Stohner, J. *Chimia* **2005**, *59*, 530.
(4) Schwerdtfeger, P.; Laerdahl, J. K.; Chardonnet, C. *Phys. Rev. A* **2002**, *65*, 042508.
(5) Crassous, J.; Collet, A. *Enantiomer* **2000**, *5*, 429.
(6) Schreiner, P. R.; Fokin, A. A.; Lauenstein, O.; Okamoto, Y.; Wakita, T.; Rinderspacher, C.; Robinson, G. H.; Vohs, J. K.; Campana, C. F. *J. Am. Chem. Soc.* **2002**, *124*, 13348.
(7) (a) Schreiner, P. R.; Lauenstein, O.; Kolomitsyn, I. V.; Nadi, S.; Fokin, A. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 1895. (b) Lauenstein, O.; Fokin, A. A.; Schreiner, P. R. *Org. Lett.* **2000**, *2*, 2201. (c) Schreiner, P. R.; Lauenstein, O.; Butova, E. D.; Gunchenko, P. A.; Kolomitsin, I. V.; Wittkopp, A.; Feder, G.; Fokin, A. A. *Chem.*−*Eur. J.* **2001**, *7*, 4996.
(8) Fokin, A. A.; Lauenstein, O.; Gunchenko, P. A.; Schreiner, P. R. *J. Am. Chem. Soc.* **2001**, *123*, 1842.
(9) de Meijere, A.; Lee, C. H.; Kuznetsov, M. A.; Gusev, D. V.; Kozhushkov, S. I.; Fokin, A. A.; Schreiner, P. R. *Chem.*−*Eur. J.* **2005**, *11*, 6175.
(10) (a) Tsanaktsidis, J.; Eaton, P. E. *Tetrahedron Lett.* **1989**, 6967. (b) Della, E. W.; Head, N. J.; Mallon, P.; Walton, J. C. *J. Am. Chem. Soc.* **1992**, *114*, 10730.
(11) (a) Lukin, K. A.; Li, J.; Eaton, P. E.; Kanomata, N.; Hain, J.; Punzalan, E.; Gilardi, R. *J. Am. Chem. Soc.* **1997**, *119*, 9591. (b) Hrovat, D. A.; Borden, W. T. *J. Am. Chem. Soc.* **1994**, *116*, 6459.
(12) Della, E. W.; Head, N. J.; Mallon, P.; Walton, J. C. *J. Am. Chem. Soc.* **1992**, *114*, 10730.
(13) Fokin, A. A.; Schreiner, P. R. *Chem. Rev.* **2002**, *102*, 1551.
(14) Liguori, L.; Bjørsvik, H.-R.; Bravo, A.; Fontana, F.; Minisci, F. *Chem. Commun.* **1997**, 1501.
(15) (a) Berger, R.; van Wüllen, C. *J. Chem. Phys.* **2005**, *122*, 134316. (b) Berger, R.; Langermann, N.; van Wüllen, C. *Phys. Rev. A* **2005**, *71*, 042105.
(16) (a) Häser, M.; Ahlrichs, R. *J. Comput. Chem.* **1989**, *10*, 104. (b) Ahlrichs, R.; Bär, M.; Häser, M.; Horn, H.; Kölmel, C. *Chem. Phys. Lett.* **1989**, *162*, 165.
(17) Frisch, M. J.; et al. *Gaussian03*; revision B.03; Gaussian Inc.: Pittsburgh, PA, 2003; see Supporting Information for full reference.
(18) Laerdahl, J. K.; Schwerdtfeger, P.; Quiney, H. M. *Phys. Rev. Lett.* **2000**, *84*, 3811.
(19) Crassous, J.; Jiang, Z.; Schurig, V.; Polavarapu, P. L. *Tetrahedron: Asymmetry* **2004**, *15*, 1995.

JA060781P