Intramolecular Kinetic Deuterium Isotope Effects on Microsomal Hydroxylation and Chemical Chlorination of Toluene-α-d_1 and Toluene-α,α-d_2

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Abstract: Deuterated toluenes $PhCH_2D$ and $PhCHD_2$ were synthesized and subjected separately to microsomal hydroxylation in vitro. Mass spectral analysis of the resulting benzyl alcohols indicated substantial excess retention of deuterium, a consequence of the combined influence of primary ($P = k_H^{HH}/k_D^{HH}$) and secondary ($S = k_H^{HH}/k_H^{HD}$) *intra*molecular kinetic isotope effects. Equations were developed which relate the expected product ratios to the values of P and S; i.e., $r_1 = d_1/d_0 = 2P/S$ (eq 7) and $r_2 = d_2/d_1 = P/2S$ (eq 8). From eq 7 and 8 it follows that in parallel experiments with **1** and **2**, r_1/r_2 should have the value 4.0. In our studies the observed value of r_1/r_2 was only 2.13 ± 0.84 ($n = 7$); moreover, this ratio did not depend upon the induction status of the microsomes. A number of potential explanations for this discrepancy were considered, but none were satisfactory. At present we have no clear explanation for this discrepancy, although part of it could be attributable to failure of the "rule of the geometric mean". Toluenes **1** and **2** were also subjected to chlorination in a simple chemical system, and data from mass spectral analysis of the resulting benzyl chlorides were used to test 7 and 8. In this case we found that $r_1 = 11.87 \pm 0.12$ and $r_2 = 2.96 \pm 0.03$; thus $r_1/r_2 = 4.01 \pm 0.07$, in excellent agreement with the predicted value. Since the *inter*molecular isotope effect for $PhCH_3/PhCD_3$ chlorination in this system, which is given by the expression $r_3 = d_0/d_2 = PS^2$ (eq 9), has the value 3.6 [Fonouni et al. *J. Am. Chem. Soc.* **1983**, *105*, 7672], eq 7-9 can be solved simultaneously, which reveals that $S = 0.85$ and $P = 5.0$. This appears to be the first time an analysis of concurrent primary and secondary isotope effects on reactions at a methyl group has been carried out. For the chlorination the large primary effect is consistent with considerable C-H bond breaking in the rate-limiting step, but the *inverse* secondary effect is unexpected, in that it appears inconsistent with simple transition states approaching the structure of a benzylic radical. At present we have no explanation for the discrepant results from the microsomal hydroxylations. We are currently exploring inter- and intramolecular isotope effects on other benzylic functionalization reactions of **1** and **2**.

There have been many attempts to employ kinetic deuterium isotope effects (KDIEs) as probes of the mechanism of cytochrome P-450 catalyzed aliphatic hydroxylations.[1] With few exceptions,[2,3] the focus of attention in these studies has been on primary KDIEs, while the potential contributions of secondary KDIEs have received much less attention. In the majority of cases the observed KDIEs were *inter*molecular in nature, coming from competition studies or separate experiments with H and D substrates, and the effects were relatively small (i.e., $1 \leq k_H/k_D \leq 3$), although larger intermolecular KDIEs have occastionally been observed.[4,5] In contrast, when experimental design has allowed the measurement of *intra*molecular KDIEs (i.e, isotopic discrimination between H and D located at otherwise identical sites in a given molecule) very large KDIEs have been observed. Examples include $k_H/k_D = 10$ for O-demethylation of p-$CH_3OC_6H_4OCD_3$,[6] and $k_H/k_D = 11$ for the benzylic hydroxylation of 1,1-dideuterio-1,3-diphenylpropane.[7] The phenomenon of metabolic switching, in which deuterium substitution at one of several alternate sites of attack within a given molecule alters the product ratios, is probably another manifestation of intramolecular discrimination among various sites of intrinsically different chemical reactivity. For example, the ratio of ortho-hydroxylation to O-demethylation is much higher with $PhOCD_3$ than with $PhOCH_3$.[8]

It has become popular in the cytochrome P-450 field to rationalize the very different magnitudes of inter- vs. intramolecular isotope effects on C-hydroxylation reactions along lines elaborated by Hjelmeland,[7] Miwa,[9] and Northrop.[10] Thus the intermolecular isotope effects seen in the usual studies may *appear* small because of "commitment to catalysis", or because the product-forming step is only partially rate-limiting in turnover. In contrast, the larger intramolecular isotope effects on C-hydroxylation reactions are thought possibly to reflect the true KDIE on the product-forming step(s) since the discrimination occurs within a single catalytic cycle rather than between successive cycles.

With these concepts in mind we sought to apply the intramolecular approach to measuring both primary and secondary KDIEs on the benzylic hydroxylation of toluene by cytochromes P-450. Toward this end we have synthesized $PhCH_2D$ (**1**) and $PhCHD_2$ (**2**), submitted them to hydroxylation by rat liver microsomes, and analyzed the resultant cresols and benzyl alcohols for their deuterium content. In addition, we have investigated H/D discrimination during side-chain monochlorination of these two substrates under conditions of phase-transfer catalysis. We report below on the results of this work.

Experimental Section

Synthesis of $PhCH_2D$ (1). Benzaldehyde (3.0 g, 28.3 mmol, freshly purified by vacuum distillation) was dissolved in 10 mL of dry tetrahydrofuran (THF) and added dropwise to a stirred suspension of $LiAlD_4$ (1.2 g, 28.3 mmol) in 4 mL of THF in a 100-mL three-necked flask. After being stirred for 2 h at room temperature the reaction was worked up by successive cautious addition of 1.2 mL of H_2O, 1.2 mL of 15% NaOH, and 3.6 mL of H_2O. The liquid phase was decanted from the granular residue, the THF removed on a rotary evaporator, and the residue chromatographed over silica gel, yielding 2.7 g of PhCHDOH (GC/MS analysis 98.6 mol % d_1, 1.4 mol % d_0). This material was dissolved in 15 mL of dry benzene and HBr gas was slowly bubbled through the solution for 2-10 min at room temperature. The conversion of benzyl alcohol to benzyl bromide was monitored by TLC (**Caution**: *the HBr procedure should be done in a very good fume hood*). The benzene solution was washed with $NaHCO_3$ solution, dried briefly over $MgSO_4$, and concentrated on a rotary evaporator. The resultant PhCHDBr was purified by three successive bulb-to-bulb distillations at 100, 40, and finally 20 torr with dry ice trapping of the distillate. The purified PhCHDBr (3 g, 17.4 mmol) was dissolved in 7 mL of hexamethyl-

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phosphortriamide (HMPA), 2.19 g of $NaCNBH_3$ (35 mmol) was added, and the mixture was stirred at 70–80 °C for 3 days. At the end of this time the $PhCH_2D$ product was removed and purified by three successive bulb-to-bulb distillations at 100 torr operating pressure. GLC analysis indicated the product to be >98% pure. The final overall yields for several preparations were in the range of 40–60%.

Synthesis of $PhCD_2H$ (2). Methyl benzoate (2.7 g, 20 mmol) was dissolved in 8 mL of dry THF and added to a suspension of $LiAlD_4$ (0.62 g, 10.7 mmol) in 4 mL of THF which was stirred overnight at room temperature. The reaction was worked up as described above and the crude $PhCD_2OH$ product chromatographed on silica gel (yield 0.97 g, 44%; GC/MS analysis 97.6 mol % d_2, 2.4 mol % d_1). This material was converted to $PhCD_2Br$, the latter reduced in HMPA with $NaCNBH_3$, and the $PhCD_2H$ product purified as described above.

Because the mass spectrum of toluene is dominated by M–H(D) fragmentation to tropylium ion, which complicates direct isotope ratio measurements, the final deuterium content of **1** and **2** was taken to be that of their synthetic precursors (i.e., the benzyl alcohols PhCHDOH and $PhCD_2OH$). Since the cresol metabolites from **1** and **2** showed the same deuterium content as these benzyl alcohols (see below), the deuterium content of toluenes **1** and **2** must have been the same as that of their synthetic precursors.

Microsomal Hydroxylations. Microsomal incubations, product isolation, and deuterium analyses were conducted as described previously[11] for cresol metabolites of toluene, except that it was not necessary to prepare trimethylsilyl derivatives of the benzyl alcohols.

Chlorination Reactions. Chlorinations were carried out with commercial Clorox as the source of hypochlorite, essentially as described by Fonouni et al.[12] The deuterated toluene (90 μL) was dissolved in 3.1 mL of CH_2Cl_2, and 1 mL of this solution was placed in each of three 13 × 100 mm culture tubes fitted with Teflon-lined screwcaps. Clorox was acidified to pH 8.8 with 10% HCl, and 2.8 mL was added to each tube, followed by 19 mg of solid Bu_4NHSO_4. Each tube was then flushed with N_2 for 5 s and stirred vigorously for 10 min at 25 °C, after which stirring was stopped and the aqueous phase removed by pipet. Pentane (3 mL) was added to the organic layer and the solution washed with water, bisulfite solution, and water again (3 mL each time) and finally dried with anhydrous $MgSO_4$. GLC analyses (3% OV-17, 2 mm × 2 m packed column, 100 °C) indicated conversions of 5–10% after 10 min. The product consisted mainly of benzyl chloride (>90%, R_t 6.9–7.2 min) along with small amounts of ring-chlorinated toluene isomers (R_t 3.7–4.2 min). After 10 min of reaction benzal chloride (R_t = 19.5 min) was only detected in trace quantities by GC/MS analysis, although at longer times (e.g., 30–240 min) it amounted to 5–20% of the product; benzyl alcohol and benzaldehyde were not detected.

Results and Discussion

The microsomal hydroxylation of toluene leads mainly to benzyl alcohol (50–88% of products) along with lesser amounts of *o*-, *m*-, and *p*-cresols; the actual product ratios vary depending on the induction status of the microsomes.[11] Control incubations established that benzaldehyde and benzoic acid accounted for less than 1% of the total products formed from unlabeled toluene. Furthermore, the amount of d_0 benzyl alcohol produced from **2** was never more than 3 mol % over the amount of d_1 impurity present in **2**, which rules out the possibility of significant loss of deuterium from the benzyl alcohol metabolites through redox interconversion with benzaldehyde (cf. ref 13 and 14). Finally in each incubation of **1** or **2** the deuterium content of the three isomeric cresol metabolites formed was identical within experimental error (±2%) with that of the starting toluenes (data not shown; cf. ref 11). Other control experiments using chemically synthesized PhCHDOH and $PhCD_2OH$ established that there were no detectable deuterium isotope effects on the mass spectral fragmentation of benzyl alcohol. Finally, no deuterium was ever observed in the phenyl peak [$C_6H_5^+$] in the mass spectrum of the benzyl alcohol metabolites, indicating the absence of rearrangements during microsomal hydroxylation and mass spectral fragmentation. The deuterium analyses of the benzyl alcohol metabolites from **1** and **2** are reported in Table I, lines 1–7.

Table I. Deuterium Content of Benzyl Alcohol Metabolite from $PhCH_2D$ (**1**) and $PhCHD_2$ (**2**)

		deuterium content of BzOH metabolite	
expt	microsome type[a]	from **1** mol % d_1	from **2** mol % d_2
1	AC	80.2	67.2
2	AC	90.8[b]	76.0
3	AC	84.2	68.9
4	PB	79.2	70.7
5	PB	87.0	79.0[b]
6	UT	84.7	72.6
7	UT	85.9	72.1
mean ± SD	(n = 7)	84.57 ± 3.97	72.35 ± 4.06
8	AC	83.7	71.4
9	PB	90.5	75.2
10	PB	88.9	73.5
mean ± SD	(n = 3)	87.70 ± 3.55	73.36 ± 1.90
mean ± SD	(n = 10)	85.51 ± 3.95	72.66 ± 3.46

[a] AC, Aroclor-1254 induced; PB, phenobarbital induced; UT, untreated (control). [b] These values were examined by means of an outlier determination test (Hewlett-Packard Stat-Pac) and found not to be outliers. Hence, they were not excluded.

If there were no discrimination between hydrogen and deuterium (i.e., purely statistical loss of H or D), the benzyl alcohol produced from **1** and **2** should have contained 65.73 mol % d_1 and 32.53 mol % d_2, respectively, after correction for the deuterium content of the substrates. However, the data in Table I clearly show that there was preferential loss of hydrogen during the benzylic hydroxylation of toluenes **1** and **2**. As indicated in Table I, an outlier test was used to examine values which appeared to be out of line with the others, but since the test did not show them to be outliers, all the data in the table were averaged and used in subsequent calculations. It is also noteworthy that the induction status of the microsomes had no apparent effect on the isotopic discrimination that occurred during the hydroxylation. This is consistent with the emerging view that fundamental aspects of mechanism are conserved among various forms of mammalian[11,15] and bacterial[16,17] cytochrome P-450.

An attempt to treat these data quantitatively begins with the model described by eq 1 and 2, which relate the corrected product ratios r_1 and r_2 to the ratios of specific rate constants for the bond cleavages indicated by the dashes in the associated structural formulae. In this formalism a simple primary KDIE would be represented by the ratio $P = k_H^{HH}/k_D^{HH}$ and a simple α-secondary KDIE would be given by the ratio $S = k_H^{HH}/k_H^{HD}$. In fact it was the objective of our experiments to determine the values of P and S for the benzylic hydroxylation of toluene. If one then assumes that primary and secondary isotope effects contribute independently of one another (i.e., assume that the "rule of geometric mean" or RGM obtains), one can also write the expressions given in eq 4–6. Substituting these expressions through eq 1–3 leads to eq 7–9, respectively.

$$\frac{2(\text{PhCHD–H})}{(\text{PhCHH–D})} = \frac{d_1}{d_0} = 2k_H^{HD}/k_D^{HH} = r_1 \quad (1)$$

$$\frac{(\text{PhCDD–H})}{2(\text{PhCHD–D})} = \frac{d_2}{d_1} = k_H^{DD}/2k_D^{HD} = r_2 \quad (2)$$

$$\frac{(\text{PhCHH–H})}{(\text{PhCDD–D})} = \frac{d_0}{d_2} = k_H^{HH}/k_D^{DD} = r_3 \quad (3)$$

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$$P = \frac{k_H^{HH}}{k_D^{HH}} = \frac{k_H^{HD}}{k_D^{KD}} = \frac{k_H^{HD}}{k_D^{DD}} \quad (4)$$

$$S = \frac{k_H^{HH}}{k_H^{HD}} = \frac{k_D^{HH}}{k_D^{HD}} = \frac{k_H^{HD}}{k_H^{DD}} \quad (5)$$

$$S^2 = \frac{k_H^{HH}}{k_H^{DD}} = \frac{k_D^{HH}}{k_D^{DD}} \quad (6)$$

$$r_1 = d_1/d_0 = 2P/S \quad (7)$$

$$r_2 = d_2/d_1 = P/2S \quad (8)$$

$$r_3 = d_0/d_2 = PS^2 \quad (9)$$

Although both eq 7 and 8 are linear equations which intersect at the origin, they can at least be solved for the ratio of their slopes, r_1/r_2, which is simply 4. From the means of the data from experiments 1–7 (Table I), the values of r_1 and r_2, corrected for the d_0 material in **1** and the d_1 material in **2**, are given by the expressions $r_1 = (0.8457)/[(1 - 0.08457) - (0.0140)]$ and $r_2 = (0.7235)/[(1 - 0.7235) - (0.8457)(0.0240)]$. After propagation of errors[18] the values of r_1 and r_2 (mean ± SD) are 6.03 ± 1.99 and 2.82 ± 0.61, respectively, as given in line 1 of Table II. Thus from eq 7 and 8, the apparent net isotope effects (i.e., P/S) for the benzylic hydroxylation of **1** and **2** are 3.01 and 5.64, respectively.

These results are surprising for two reasons. First, these isotope effects are noticeably smaller than the (net) intramolecular isotope effects of 7–11 reported for other C-hydroxylations (see above) and the intrinsic isotope effects of 12.8–14.0 reported for the O-deethylation of 7-ethoxycoumarin.[19] Second, and perhaps most disturbing, they are not equal; in fact the value of r_1/r_2 is 2.13 ± 0.84, which is quite different from the expected value of 4 deduced above.

Several possible reasons can be considered to account for this discrepancy between theory and experiment. One is that perhaps the RGM does not hold and that eq 4–6 are not valid as assumed. Although the RGM is generally believed to be valid and has been widely accepted by others,[20] recent quantum mechanical calculations[21,22] suggest that violations on the order of ca. 10% may be expected. A key feature of these calculations is the assumption of strong coupling beween the in-plane and in-flight protons, together with a significant amount of nuclear tunneling for in-flight H. In agreement with these calculations, Ostovic et al.[23] observed that for hydrogen transfer among NAD^+ analogues, the secondary isotope effect on transferring H is larger than the secondary effect on transferring D by 7–10%. If we assume failure of the RGM such that the secondary effect on transferring H is 10% greater than that on transferring D, the predicted value of r_1/r_2 becomes 4.4, which is still considerably larger than the observed values of r_1/r_2 given in Table II. Unfortunately, the contrast between experiment and theory is softened somewhat by the variance associated with the data in Table I and the propagated standard deviations reported in Table II (this aspect will be discussed further below). Nevertheless, it still appears unlikely that failure of the RGM, coupling of in-place and in-flight proton motions, or nuclear tunneling can account for a discrepancy in the value of r_1/r_2 as large as observed here, although these could certainly be contributing factors.

Another possible explanation is that the apparent isotope effects observed on the hydroxylation of **1** and **2** may be a composite of the usual type of primary and secondary KDIEs, plus a contribution from a *magnetic* isotope effect. Aliphatic hydroxylation by cytochrome P-450 enzymes is usually discussed in terms of radical abstraction–recombination processes.[16,24–28] It is firmly established that the efficiency of radical recombination processes can be altered through the effects of nearby magnetic isotopes or external magnetic fields on the ease of spin inversion or intersystem crossing.[29] In such cases significant chemical fractionation of magnetic from nonmagnetic isotopes (e.g., ^2H vs. ^1H) can occur, giving rise to an apparent "isotope effect". Since such effects are usually ablated in the presence of an external magnetic field, we examined the microsomal hydroxylation of **1** and **2** in the field of a Bruker WP-80 NMR spectrometer (18.8 kGauss). The results of these experiments (Table I, lines 8–10) were not significantly different from those obtained in the absence of the NMR magnetic field (Table I, lines 1–7). Thus it would appear that the discrepancy noted above cannot be attributed to the supervention of magnetic isotope effects (although the failure to observe a magnetic isotope effect on the hydroxylation of **1** and **2** should not necessarily be taken to suggest that radical processes are not involved in cytochrome P-450 reactions).

Other factors which have been considered seem even less likely to account for the difference in the isotope effects seen with **1** and **2**. Committment to catalysis can suppress the expression of an intrinsic isotope effect,[10] but it is not clear why this should be different for **1** vs. **2**. Suppression of a (presumably) large intrinsic isotope effect could also occur if rotation about the phenyl–methyl bond were restricted upon binding to the enzyme, but this seems relatively implausible given the apparently large active site of P-450 enzymes. Furthermore, the substantially different isotope effects observed with **1** and **2** would require substantial differences (i.e., a large isotope effect) in their binding, which seems even less plausible. Conceivably there could have been different degrees of metabolic switching from methyl- to ring-hydroxylation with **1** and **2**. Although our assay procedures were optimized for measurement of isotope ratios rather than product ratios, major effects (>10%) would likely have been noticed, but none were. In any case metabolic switching per se should not have affected H/D discrimination during the methyl hydroxylation which did occur with **1** and **2**.

At this point we decided to test eq 1–9 using data from a simple chemical model reaction system. To obtain such data toluenes **1** and **2** were separately subjected to chlorination in a nonenzymic phase-transfer system recently described by Fonouni et al.[12] In this system the intermolecular isotope effect (i.e., r_3) on chlori-

Table II. Results of Analysis of Microsomal Hydroxylation Data[a]

expts	r_1	r_2	r_1/r_2	different from 4.0[b]
1–7	6.03 ± 1.99	2.82 ± 0.61	2.13 ± 0.84	0.026
8–10	8.05 ± 2.95	2.99 ± 0.31	2.69 ± 1.02	0.201
1–10	6.53 ± 2.27	2.87 ± 0.53	2.27 ± 0.90	0.054

[a] There are no significant differences within any of the columns. The standard deviations reported here were derived by propagation of the errors associated with r_1 and r_2, treating them as dependent variables; see p 128 of ref 18. [b] Probability that difference can be accounted for by experimental error; $p <$ value given.

Table III. Deuterium Retention during Chlorination of $PhCH_2D$ (**1**) and $PhCHD_2$ (**2**)

	deuterium content of BzCl	
expt	from **1** mol % d_1	from **2** mol % d_2
1	90.97	72.87
2	91.00	73.11
3	90.85	73.39
mean ± SD	90.94 ± 0.08	73.12 ± 0.26

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nation of $PhCH_3$ vs. $PhCD_3$ is 3.6, and the chlorination of ring-substituted toluenes is characterized by a Hammett ρ^+ value of −1.7. The H-abstracting agent in this system is believed to be the ClO· radical. For comparison, a Hammett ρ value of −1.6 has been reported for the cumene hydroperoxide supported P-450 catalyzed benzylic hydroxylation of substituted toluenes.[30] The isotope analyses of the benzyl chlorides resulting from the phase-transfer chlorinations of **1** and **2** are given in Table III. Processing of these data as described for the hydroxylation data reveals that $r_1 = 11.87 \pm 0.12$ and $r_2 = 2.96 \pm 0.03$; thus $r_1/r_2 = 4.01 \pm 0.07$, which is in excellent agreement with the predicted value.

In light of this result is is interesting to compare the chlorination data to the hydroxylation data directly. One immediately notices that the hydroxylation data have a much greater variance than the chlorination data. Such variance in data derived from microsomal systems is not atypical,[3,5-7,12,16,25] but as mentioned above it softens the contrast between theory and experiment. It is also interesting that both systems gave nearly identical results with toluene **2**, which means that most of the difference in the r_1/r_2 values derived from these two data sets derives from differences in the data for substrate **1**. In absolute terms this difference is only about 5 mol %, but since this is only slightly more than the relative standard deviation of the hydroxylation data, statistical analyses were performed to test the hypothesis that differences between the observed r_1/r_2 values (Table II) and the predicted values are due to random experimental error. The results of these analyses (p values) are reported in Table II; they indicate that it is rather unlikely that random errors can account for the difference between theory and experiment.

Returning now to the chlorination data with the information that $r_3 = 3.6$,[12] we can solve eq 7–9 for explicit values of P and S rather than only their ratio, whereupon we find that $P = 5.01$ and $S = 0.85$ per deuterium. The value of 5.0 for P appears quite reasonable for a primary kinetic deuterium isotope effect on a hydrogen-abstraction reaction. The finding that the secondary effect is *inverse* is somewhat surprising. Ordinarily one would expect a *normal* secondary effect as the hybridization at the benzylic carbon changes from sp^3 toward sp^2. While the exact value of S is subject to some experimental uncertainty, it would require a combination of unrealistically large errors in r_1, r_2, and r_3 for S to approach unity or greater. Furthermore, although S may be inverse, its value is not unrealistically small. Thus it would appear that there is substantial C–H bond breaking in the transition state for the rate-limiting step in the chlorination sequence and that the bonding of the secondary hydrogens is becoming tighter rather than looser. This could possibly be explained by approach of the H-abstracting species in such a way as to impede the out-of-plane bending motions of the secondary hydrogens. Other explanations may also be possible, however.

In conclusion, it would appear from the chlorination results that eq 1–9 represent a reasonable model for the analysis of *concurrent* primary and secondary kinetic deuterium isotope effects at a methyl group reaction center. Their failure to accommodate data for the microsomal hydroxylation of toluene is surprising, and at present we have no logical explanation for this. Further studies with other reagents that lead to the benzylic functionalization of toluene are planned.

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Registry No. $PhCH_2D$, 1861-00-3; $PhCHD_2$, 17117-69-6; D_2, 7782-39-0; PhCHO, 100-52-7; PhCHDOH, 4546-45-6; $PhCH_2Br$, 100-39-0; PhC(O)OMe, 93-58-3; $PhCD_2OH$, 21175-64-4; $PhCD_2Br$, 51271-29-5; cytochrome P-450, 9035-51-2.

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Synthesis and Crystal Structure of an Enantiomerically Pure, Internally Coordinated Alkylchloroborane. The Boron-Centered Anomeric Effect

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Abstract: The synthesis and crystal structure of (*S*)-(*O*–*B*)-chloro[(1*S*,2*R*,3*S*,5*S*)-2-[2(*R*)-methoxyethyl]-6,6-dimethyl-3-norpinyl]borane, an enantiomerically pure, internally coordinated alkylchloroborane monomer, are described. This is the first crystallographic structure determination for a chiral organoborane, and the first complete X-ray analysis of a monoborane–ether complex. The crystals are monoclinic of space group $P2_1$, with $Z = 2$ in a unit cell of dimensions $a = 7.468$ (3) Å, $b = 10.887$ (3) Å, $c = 7.898$ (3) Å, and $\beta = 95.29$ (3)°. The structure was determined by a heavy atom method from 1676 unique reflections and refined to a final R value of 0.046. Key features of the structure, including the configuration of the stereogenic boron atom, the unusually long B–Cl bond ($d = 1.890$ Å), and the geometry of the trivalent oxygen, are manifestations of a novel boron-centered anomeric effect. An improved preparation of $BH_2Cl{\cdot}SMe_2$ has also been devised.

Chiral organoboranes are versatile and effective reagents for asymmetric synthesis of organic structures.[1,2] We are investigating a new approach to asymmetric hydroboration of alkenes. In this process, a chiral borane A adds selectively to one face of a prochiral alkene B, affording an intermediate organoborane C which contains one or two new tetrahedral stereocenters. Further transformations of C furnish alcohols and other structurally diverse products D (X = OH or other functional group) in non-racemic form.

(1) Asymmetric hydroboration: (a) Brown, H. C.; Singaram, B.; Cole, T. E. *J. Am. Chem. Soc.* **1985**, *107*, 460–464 and references cited therein. (b) Brown, H. C.; Jadhav, P. K. In "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, Chapter 1. (c) Brown, H. C.; Jadhav, P. K.; Mandal, A. K. *Tetrahedron* **1981**, *37*, 3547–3587.

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