**Acknowledgment**. Support of this work by the National Science Foundation (CHE 81-17046), the Research Corp. and the donors of the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged. We also thank Dr. Brian Dixon of the Dow Chemical Co. for providing low resolution mass spectral data, Dr. W. Hammond of Allied-Signal Corp. for 400-MHZ and 2-D NMR data, and Drs. G. B. Schuster and M. S. Platz for providing preprints of their work on 9-xanthylidene and 1-NC.

**Registry** No. D$_2$, 7782-39-0; 1-naphthyldiazomethane, 10378-55-9; cyclohexane, 110-82-7; toluene, 108-88-3; 1-naphthylcarbene, 4399-95-5; 4-methyl-7-(1-naphthyl)cycloheptatriene, 108834-96-4; 3-methyl-7-(1-naphthyl)cycloheptatriene, 108834-97-5; 2-methyl-7-(1-naphthyl)cycloheptatriene, 108834-98-6.

# Primary and Secondary Kinetic Deuterium Isotope Effects and Transition-State Structures for Benzylic Chlorination and Bromination of Toluene

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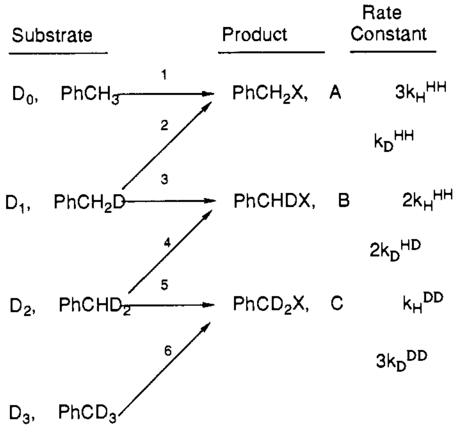
**Abstract**: As a chemical model for benzylic hydroxylations effected by cytochrome P-450 enzymes, the chlorination of PhCH$_3$, PhCH$_2$D, PhCHD$_2$, and PhCD$_3$ in a two-phase system of hypochlorite/CH$_2$Cl$_2$ with a phase-transfer catalyst has been investigated. On the basis of the deuterium content of the product benzyl chlorides, *relative* rate constants were deduced for all possible H- and D-abstractions with these substrates. From this the primary (P) and secondary (S) KDIEs were found to be 5.90 ± 0.41 and 1.03 ± 0.02, respectively, and the "rule of the geometric mean" was found to be closely obeyed. For the analogous bromination of toluene by *N*-bromosuccinimide in CCl$_4$, P and S were 6.37 ± 0.43 and 1.05 ± 0.01. The transition states of these processes must therefore involve extensive C–H bond breaking but relatively little rehybridization toward planarity at the reacting carbon.

Cytochrome P-450 is a family of mixed function oxidase enzymes that play vital roles in the biotransformation of both endogenous and xenobiotic compounds. Several types of oxygenations of organic substrates are known to be affected, depending on the structure and reactivity of the substrate. Among them aliphatic hydroxylation is particularly interesting to chemists because of the conspicuous lack of chemical reagents for effecting this transformation smoothly with molecular oxygen as the oxidant. Current hypotheses concerning the mechanism of P-450 catalyzed aliphatic hydroxylation envision two major stages.[1,2] The first involves "activation" of O$_2$ by reductive cleavage to form one molecule of water and an oxoheme or ferryl group. This process is thought to be common to all oxygenations catalyzed by P-450. In the case of *aliphatic* hydroxylation, the second is thought to involve a hydrogen abstraction/hydroxyl recombination step with a transient (caged) radical intermediate.

We have been interested in exploring the mechanism of P-450 catalyzed oxygenation processes through the use of "probe" substrates that either possess unusual electronic structures[3-5] or are substituted with deuterium.[6,7] Recently we examined the P-450 catalyzed benzylic hydroxylation of toluene-*7-d*$_1$ and toluene-*7,7-d*$_2$ to benzyl alcohol.[8] A set of model equations was devised to deconvolute the product isotope content data into values for the primary and secondary kinetic deuterium isotope effects (KDIEs) for this particular hydroxylation. Although the data showed strong preference for abstraction of hydrogen over deuterium, the model equations failed to deconvolute the data in the manner intended. However, the model *did* appear to work satisfactorily when applied to isotope discrimination data for the *chemical chlorination* of the same two deuteriated toluenes. In this case it yielded a primary KDIE of 5.0, but surprisingly, the value calculated for the secondary KDIE was 0.85, i.e., *inverse* rather than normal as might have been expected. Several possible explanations for this result were considered but none were satisfactory.

**Scheme I**



In the present work we have refined our model equations so that they now take into account inter- as well as intramolecular isotope effects, and we have re-examined the chlorination of the entire series of toluenes PhCH$_n$D$_{3-n}$ ($n$ = 0–3). Our new model (Scheme I) is found to accommodate all our data to a high degree of precision. It allows us to determine relative rate constants for all six possible H or D abstractions from the various toluenes. For this reaction the effects of deuterium substitution are seen to obey the rule of the geometric mean quite closely. The values for $P$ and $S$, the primary and secondary KDIEs, are found to be 5.90 ± 0.41 and 1.034 ± 0.019, respectively, and the reason for the *apparent* inverse secondary KDIE from the earlier model has been identified. The values of $S$ and $P$ for the bromination of toluene with *N*-bromosuccinimide are not significantly different from those

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for chlorination. Finally, the isotope effects on toluene halogenation have been related to pre-existing kinetic data and used to construct a picture of the transition state for hydrogen abstraction by the halogenating agent.

## Theory

The benzylic functionalization of toluenes $D_0$–$D_3$ involves six possible hydrogen or deuterium abstractions. These are shown in Scheme I, along with their statistically weighted rate constants. These six rate constants can be combined to define three primary and four secondary kinetic deuterium isotope effects as indicated below. The three primary effects differ according to whether there are 0, 1, or 2 deuterium atoms as "spectators" in secondary positions, while the secondary effects differ according to whether H or D is in the transferring position and whether or not there is an additional D as a spectator in the other secondary position. According to the "rule of the geometric mean" all three primary effects should be equal, and all four secondary effects should be equal.

$$P_1 = k_{\mathrm{H}}^{\mathrm{HH}}/k_{\mathrm{D}}^{\mathrm{HH}} \qquad P_2 = k_{\mathrm{H}}^{\mathrm{HD}}/k_{\mathrm{D}}^{\mathrm{HD}} \qquad P_3 = k_{\mathrm{H}}^{\mathrm{DD}}/k_{\mathrm{D}}^{\mathrm{DD}}$$

$$S_1 = k_{\mathrm{H}}^{\mathrm{HH}}/k_{\mathrm{H}}^{\mathrm{HD}} \qquad S_2 = k_{\mathrm{H}}^{\mathrm{HD}}/k_{\mathrm{H}}^{\mathrm{DD}}$$

$$S_3 = k_{\mathrm{D}}^{\mathrm{HH}}/k_{\mathrm{D}}^{\mathrm{HD}} \qquad S_4 = k_{\mathrm{D}}^{\mathrm{HD}}/k_{\mathrm{D}}^{\mathrm{DD}}$$

For any benzylic oxidation represented by Scheme I, this hypothesis can be tested by determining and comparing values for $P_1$–$P_3$ and $S_1$–$S_4$. We have approached this task through competition kinetic experiments, which can yield *relative* rate constants with a high degree of precision. The halogenation of toluenes $D_1$ and $D_2$ involves *intra*molecular isotopic discrimination, but the isotope effects $k_{\mathrm{H}}^{\mathrm{HD}}/k_{\mathrm{D}}^{\mathrm{HH}}$ and $k_{\mathrm{H}}^{\mathrm{DD}}/k_{\mathrm{D}}^{\mathrm{HD}}$ can not be related to $P$ and $S$ without *assuming* the RGM obtains. A more powerful approach is to take advantage of combined inter- and intramolecular competition experiments, specifically $D_0/D_1$, $D_1/D_2$, $D_2/D_3$, and $D_0/D_3$. One then observes the product mole ratios ($a/b$, $b/c$, $a/c$) as a function of the mole ratio of starting materials ($d_0/d_1$, $d_1/d_2$, $d_2/d_3$, or $d_0/d_3$). Under pseudo-first-order conditions the product ratios are in all cases *linear* functions of the starting material ratios, and the rate constants listed in Scheme I can be determined from the slopes and intercepts of the appropriate plots. Further details are given in the Appendix.

## Experimental Section

**Syntheses of Deuteriated Toluenes.** Toluene-*7*-$d_1$ was prepared by refluxing benzyl bromide (8.04 g, 47 mmol) with $LiAlD_4$ (0.5 g, 23.5 mmol) in 50 mL $Et_2O$ overnight. GLC analysis indicated complete reduction. The reaction was quenched cautiously with water and the ether layer dried ($MgSO_4$). Fractional distillation was used to remove the ether and to isolate the toluene-$d_1$. Toluene-*7,7*-$d_2$ and -*7,7,7*-$d_3$ were prepared by reducing methyl benzoate with $LiAlD_4$ in ether to obtain $PhCD_2OH$. The latter was brominated by treatment with 1.5 equiv of $PBr_3$ in $CH_2Cl_2$ at -20 to -10 °C for 3 h, after which the solution was washed with water and $NaHCO_3$ solution and dried ($MgSO_4$) and the $CH_2Cl_2$ removed by fractional distillation to give a colorless residue of $PhCD_2Br$ (which was not distilled) in essentially quantitative yield. The latter was then reduced with either $LiAlH_4$ or $LiAlD_4$ in ether as described above to afford toluene-$d_2$ and toluene-$d_3$, respectively. All toluenes were purified by distillation prior to use.

**Phase-Transfer-Catalyzed (PTC) Chlorination Reactions.** Solutions of toluene mixtures (e.g., $D_0/D_1$, $D_1/D_2$, etc.) were prepared by using a microliter syringe to deliver appropriate amounts of the individual toluenes such that the total concentration of toluene in all solutions was 30 μL/mL of $CH_2Cl_2$. In all cases the toluene with the greatest number of deuteriums was the major component. The exact isotopic composition of each mixture was determined by GC/MS analysis at 12 eV as described below. Samples of these solutions were stirred vigorously with an aqueous solution of hypochlorite plus a phase-transfer catalyst for 10 min and quenched is described previously.[8,9] Conversions were usually around 5% and never more than 10%.

**Brominations.** Solutions of toluenes $D_0$ and $D_1$ in $CCl_4$ were prepared as for the chlorination reaction. One milliliter of each solution was added to 4.5 mg of *N*-bromosuccinimide (0.067 equiv), sealed in a teflon-lined screw cap vial, and heated at 105 °C for 60 min. After the mixture was cooled 1 mL of hexane was added to precipitate the succinimide, and the solutions were subjected to GC/MS analysis.

**Table I.** Slopes and Intercepts of Plots Relating Benzyl Halide Product Composition to Deuteriated Toluene Substrate Composition

| expt | eq[a] | slope[b] | intercept[b] | *r* | *n* |
|---|---|---|---|---|---|
| | | Chlorination | | | |
| $D_0/D_1$ | 3 | 1.538 ± 0.022 | 0.0890 ± 0.0150 | 0.9996 | 6 |
| $D_1/D_2$ | 10 | 1.931 ± 0.032 | 11.500 ± 0.050 | 0.9997 | 4 |
| $D_1/D_2$ | 14 | 2.134 ± 0.012 | 0.3476 ± 0.0072 | 0.9999 | 4 |
| $D_2/D_3$ | 20 | 1.557 ± 0.012 | 2.881 ± 0.0372 | 0.9999 | 5 |
| $D_0/D_3$ | 24 | 0.166 ± 0.005 | | | 4 |
| | | Bromination | | | |
| $D_0/D_1$ | 3 | 1.582 ± 0.009 | 0.0827 ± 0.0055 | 0.9999 | 4 |

[a] Equation used (see Appendix). [b] Results given as mean ± SD.

**Table II.** Values of Primary and Secondary Isotope Effects for Halogenation of Toluenes[a]

| eq[b] | isotope effect | value | eq[b] | isotope effect | value |
|---|---|---|---|---|---|
| | | Chlorination | | | |
| 7 | $P_1$ | 5.76 ± 0.97 | 6 | $S_1$ | 1.025 ± 0.015 |
| 13 | $P_1$ | 5.90 ± 0.09 | 15 | $S_2$ | 1.067 ± 0.006 |
| 11 | $P_2$ | 5.96 ± 0.10 | 12 | $S_3$ | 1.036 ± 0.033 |
| 16 | $P_2$ | 6.14 ± 0.13 | 17 | $S_3$ | 1.068 ± 0.022 |
| 23 | $P_2$ | 6.15 ± 0.08 | 22 | $S_4$ | 0.976 ± 0.017 |
| 21 | $P_3$ | 5.75 ± 0.14 | | | |
| | mean | 5.90 ± 0.41 | | | 1.034 ± 0.019 |
| | | Bromination | | | |
| 7 | $P_1$ | 6.37 ± 0.43 | 6 | $S_1$ | 1.055 ± 0.006 |

[a] Results given as mean ± SD. [b] Equation used for calculation (see Appendix).

**Mass Spectral Analysis for Deuterium.** Samples were introduced to a Nermag R10-10b quadrupole mass spectrometer via a DB-5 capillary GC column. Data for the molecular ion region were collected in the selected ion mode with use of ionization energies of 12 eV for the toluenes and 14 eV for the halides. The latter proved to be quite important as it essentially eliminated the M-H fragmentation which becomes important at 70 eV. Mass spectral peak intensity data were analyzed by using the matrix algebraic method of Brauman.[7,8,10] In this method a matrix of peak intensity data is constructed for the unlabeled compound (the **A** matrix) and related to another matrix of peak intensity data for the mixture of labeled compounds (the **P** matrix) by means of the equation $\mathbf{A}\cdot\mathbf{X} = \mathbf{P}$, where **X** is a matrix containing the mole fractions of each of the components in the mixture. Solving this matrix equation gives $\mathbf{X} = (\mathbf{A}^{\mathrm{T}}\mathbf{A})^{-1}\mathbf{A}^{\mathrm{T}}\mathbf{P}$, and the individual values in the **X** matrix give least-squares values for the mole fractions of components in the mixture.

**Data Analysis.** Data are reported as mean values ± one standard deviation. Calculations were performed with full propagation of errors.

## Results

Data for the isotopic composition of the benzyl halide products and their respective toluene precursors were related by linear regression analysis with use of eq 3, 10, 14, 20, and 24 as appropriate (see Appendix). In all cases excellent fits were obtained, and the resulting slopes and intercepts are summarized in Table I. For each competition experiment the equations indicated in Table II were used to calculate the isotope effects $P_1 - S_4$ as defined above, and these results are presented in Table II.

For the chlorinations it is clear that all the primary DIEs are very nearly identical, their combined average being 5.90 ± 0.41. The secondary DIEs are quite small and in general do not appear to differ appreciably or in any systematic way. Thus, as inferred from our previous studies with $D_1$ and $D_2$, toluene chlorination appears to follow the "rule of the geometric mean" very closely.

Isotope effect data for the bromination of toluene are also given in Tables I and II. The values of $P_1$ and $S_1$ for this reaction are not significantly different from the mean values of $P$ and $S$ for the chlorination reaction.

From the data of Table II it is possible to calculate *relative* values for the individual rate constants involved in Scheme I, and

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(9) Fonouni, H. E.; Krishnan, S.; Kuhn, D. G.; Hamilton, G. A. *J. Am. Chem. Soc.* **1983**, *105*, 7672–7676.

(10) Brauman, J. I. *Anal. Chem.* **1966**, *38*, 607–610.

**Table III.** Relative Rate Constants for PTC Chlorination of Toluenes[a]

| reaction[b] | | relative rate | reaction[b] | | relative rate |
|---|---|---|---|---|---|
| 1 | $k_{\mathrm{H}}^{\mathrm{HH}}$ | (1.000) | 4 | $k_{\mathrm{D}}^{\mathrm{HH}}$ | 0.170 ± 0.011 |
| 2 | $k_{\mathrm{H}}^{\mathrm{HD}}$ | 0.967 ± 0.017 | 5 | $k_{\mathrm{D}}^{\mathrm{HD}}$ | 0.164 ± 0.007 |
| 3 | $k_{\mathrm{H}}^{\mathrm{DD}}$ | 0.935 ± 0.022 | 6 | $k_{\mathrm{D}}^{\mathrm{DD}}$ | 0.158 ± 0.011 |

[a] Data expressed as mean ± SD. [b] Refer to Scheme I.

**Table IV.** Relative Reactivities of Deuteriated Toluenes toward PTC Chlorination

| toluene | relative rate |
|---|---|
| $D_0$ | $k_{\mathrm{H}}^{\mathrm{HH}} = 1.00$ |
| $D_1$ | $(2k_{\mathrm{H}}^{\mathrm{HD}} + k_{\mathrm{H}}^{\mathrm{HH}})/3 = 0.701$ |
| $D_2$ | $(2k_{\mathrm{D}}^{\mathrm{HD}} + k_{\mathrm{H}}^{\mathrm{DD}})/3 = 0.421$ |
| $D_3$ | $k_{\mathrm{D}}^{\mathrm{DD}} = 0.158$ |

from these the effect of stepwise deuteration on the overall reactivity of the methyl group of toluene. These results are given in Tables III and IV, respectively.

## Discussion

Our primary objective in this study was to develop and validate a method for the concurrent determination of both primary and secondary KDIEs for reactions involving the functionalization of aromatic methyl groups.[8] A secondary objective was to test the "rule of the geometric mean" (RGM) by determining for the benzylic chlorination of toluene whether there was any coupling or interaction between reacting and nonreacting C–H bonds in the transition state. Our previous investigation[8] of the chlorination of $PhCH_2D$ and $PhCHD_2$ suggested that our approach was feasible and that there were no apparent violations of the RGM for this reaction. However, the value of 0.85 that our model gave for the secondary KDIE seemed incompatible with preconceived notions about transition states stabilized by benzylic resonance,[11] since for a transition state more $sp^2$-like than the initial $sp^3$ ground state, a normal (i.e., >1) rather than inverse secondary effect would be expected.[12-14]

The model depicted in Scheme I is similar to but more extensive than the one used in our previous study. In fact Scheme I represents *all* possible benzylic reactions of all possible side chain deuteriated toluenes. Provided that sufficient *independent* observations are made, all six relative rate constants can be determined. Thus all possible primary and secondary isotope effects ($P_1 - S_4$ as defined above) can be calculated and compared to test the RGM. As Tables I and II show, equations based on Scheme I (derived in the Appendix) accommodate all our data extremely well and enable us to determine both the primary and secondary KDIEs for reaction at a methyl group with three chemically equivalent hydrogens. Furthermore, this approach should be easily applicable to enzyme studies, as originally intended.[8]

The various primary isotope effects that emerge from the data (Table II) are all quite close to one another. Their mean is 5.90 ± 0.41, with most of the variance arising from the first $P_1$ valve, primarily because the $b_1$ term in the denominator of eq 7 is a rather small number with a rather large relative standard deviation. Another way of looking at apparent differences among the $P$ valves in Table II is to realize that rate *ratios* can be very sensitive to small differences in absolute rates. For example, the difference between the lowest and highest $P$ values for chlorination arises from only a 1% difference in absolute rates (i.e., $5.75 = 0.852/0.148$ and $6.15 = 0.860/0.140$). Thus for practical purposes all the primary KDIEs for the chlorination of toluene are the same.

The secondary KDIEs that emerge from the data show even less variation than the primary effects, but because the effects themselves are smaller their relative deviations are larger. In contrast to the primary effect, the secondary effects are in general quite small, their combined average being 1.034 ± 0.019 (i.e., the true effect could conceivably be as large as 1.07). The $S_1$ value appears to stand out by being inverse, but this result arises in large part because the denominator of eq 22 is again a rather small number whose relative standard deviation is somewhat larger than most others. Thus for practical purposes we believe that all secondary effects on the chlorination of toluene may be regarded as being equal and only slightly larger than one.

The *intra*molecular isotope effect $r_1 = 2k_{\mathrm{H}}^{\mathrm{HD}}/k_{\mathrm{D}}^{\mathrm{HH}}$ is given by the intercepts of eq 3 and 10 as 11.2 ± 1.9 and 11.50 ± 0.05, respectively, while the intramolecular isotope effect $r_2 = k_{\mathrm{H}}^{\mathrm{DD}}/2k_{\mathrm{D}}^{\mathrm{HD}}$ is given by the intercept of eq 20 as 2.88 ± 0.037. These extrapolated valves may be compared to the previously reported[8] directly determined valves of 11.87 ± 0.12 and 2.96 ± 0.03, respectively. It can be shown[8] that if the RGM is obeyed, the ratio $r_1/r_2$ should have the value 4. In our earlier work we found that $r_1/r_2 = 4.01 \pm 0.07$, and from the extrapolated data of this study $r_1/r_2 = 3.99 \pm 0.05$. This result establishes the reproducibility of these experiments and lends credence to the conclusion that apparent differences among $P$ values and $S$ values are due to the sensitivity of the equations to experimental error and not to violations of the RGM. Another way of viewing this is in terms of the individual rate constants compiled in Table III. Moving down the columns produces stepwise changes by a factor of 1.035 from the effect of deuterium in *secondary* positions. Moving from left to right leads to a decrease by a constant factor of 1/5.9 from the effect of deuterium in the *transferring* position.

The individual rate constants given in Table III can be combined as shown in Table IV to estimate the effect of stepwise deuteration on the *overall* reactivity of toluene. These data essentially give the intermolecular isotope effects that would be observed if the individual toluenes rather than mixtures were chlorinated. For example, the value of $k_{\mathrm{H}}^{\mathrm{HH}}/k_{\mathrm{D}}^{\mathrm{DD}}$, corresponding to the intermolecular isotope effect for chlorination of $PhCH_3$ vs. $PhCD_3$, is 6.33 ± 0.44. This is very different from the value of 3.6 reported by Fonouni et al.[9] Their isotope effect was based on independent rate measurements for the $D_0$ and $D_3$ compounds, whereas ours is based on competition kinetic experiments. Since absolute rate measurements are much harder to reproduce than competitive measurements, especially where heterogeneous reaction conditions are involved, we presume their value is in error. The use of their value in our first model turns out to be the sole cause for the unexpectedly inverse value of $S$ we obtained earlier.

The mechanism of the phase-transfer-catalyzed chlorination of toluene is not known with certainty, but it probably involves a free radical chain with $ClO^{\bullet}$ as the H-abstracing species.[9] The KDIEs given in Table III provide us with a view of the transition state for this process from the standpoint of the toluene substrate. The large primary KDIE (5.90) suggests extensive breaking of the reacting C–H bond, while the rather low value for the secondary KDIE (1.03) implies relatively little change in the out-of-plane bending motions of the nonreacting hydrogens. For the bromination of toluene by *N*-bromosuccinimide (NBS) in $CCl_4$, $P_1$ and $S_1$ (Table II) are only slightly greater than for the phase-transfer-catalyzed chlorination, which suggests there may be considerable similarity in the transition states for these reactions. The overall course of the these halogenations is suggested to be as shown in Scheme II. The transition state is apparently closer to a *pyramidal* benzyl radical than it is to a classical resonance stabilized planar[11] benzyl radical. We will return to this point later in our discussion.

Since our previous study we became aware of an earlier investigation of the halogenation of toluenes $D_1$ and $D_2$ by Wiberg and Slaugh.[15] They reported "intramolecular $k_H/k_D$" values (which appear to correspond to $r_1/2$ and $2r_2$ in our notation) but

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[11] Pacansky, J.; Liu, B.; DeFrees, D. *J. Org. Chem.* **1986**, *51*, 3720–3721.

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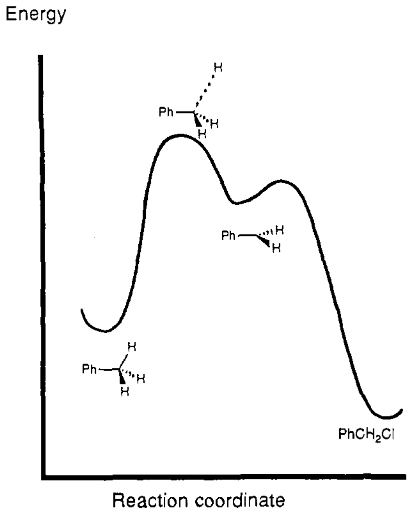
[15] Wiberg, K. B.; Slaugh, L. H. *J. Am. Chem. Soc.* **1958**, *80*, 3033–3039.

**Scheme II**



did not actually resolve *these net* intramolecular KDIEs into their component primary and secondary effects. They observed similar KDIEs for NBS and $Br_2$, and much smaller but again similar KDIEs for $Cl_2$ and $SO_2Cl_2$. From this they concluded that both brominating reagents involved bromine atom as the H-abstracting species, and both chlorinating agents involved chlorine atom as the H-abstracting species. They also observed that the KDIEs for NBS bromination of *p*-chlorotoluene, toluene, *p*-methoxytoluene, ethylbenzene, and cumene decreased monotonically in that order. Thus, in accord with the reactivity–selectivity principle, the more vigorous halogenating agents and the more reactive hydrocarbons showed the lowest KDIEs. In our studies we found that the PTC chlorination of toluene leads to KDIEs virtually identical with those for NBS bromination. Thus as suggested by Fonouni et al.,[9] the PTC chlorination of toluene most probably does not involve chlorine atom as the H-abstracting species.

Keeping in mind probable differences between chlorinations involving $Cl_2$ vs. hypochlorite/PTC, it is interesting to relate the reaction pathway depicted in Scheme II to kinetic data for the chlorination of hydrocarbons with $Cl_2$ and for the *solvolysis* of the resulting chlorides. Russell and Brown[16] showed that for a number of hydrocarbons, the relative reactivity of tertiary vs. primary hydrogens toward chlorine atom was nearly constant at a ratio of 3.5 and that C–H bonds which were both tertiary and benzylic were only about 5-fold more reactive than tertiary C–H bonds in alkanes. Further studies by Russell et al.[17] reinforced this point and led them to comment that (1) "In chlorination [with $Cl_2$], the phenyl group fails to produce an activation consistent with its effects in many other free-radical processes, or with the resonance stabilization expected for the benzyl radical", and (2) "in chlorination [with $Cl_2$] the transition state involves little breaking of the carbon–hydrogen bond and therefore is rather insensitive to resonance stabilization". The small *net* KDIEs observed [with $Cl_2$] by Wiberg and Slaugh[15] are certainly consistent with these conclusions. The small *secondary* KDIEs we report here for $OCl^-$/PTC and NBS reactions of toluene indicate this phenomenon may be more general, occurring even with less-reactive/more-selective reactants.

The solvolysis of alkyl halides involves transition states approaching the structure of a planar carbenium ion and *normal* $\alpha$-secondary KDIEs as large as 1.20 per deuterium.[12,13] Brown and Fletcher[18] observed that 3-chloro-2,3,4-trimethylpentane (I) solvolyzed 15.3-fold faster than its 2-chloro isomer (II), and they attributed this difference to the greater relief of intramolecular crowding as the C–Cl bond weakened and the central carbon assumed a more planar configuration in the transition state. In contrast they found that chlorination of the parent hydrocarbon with $Cl_2$ produced I and II in a 1:2 (i.e., statistical) ratio, implying the absence of any relief of intramolecular strain (and thus no geometrical reorganization at the reacting carbon) in the transition state.

In conclusion, we have shown that it is possible to resolve primary and secondary KDIEs for reactions at a methyl group with three equivalent hydrogens. Our observations also indicate that the KDIEs for hypochlorite/PTC chlorination of toluene are similar to those for NBS bromination but different from those for chlorination with $Cl_2$. For the former reactions the transition state involves considerable C–H bond breaking but relatively little rehybridization and benzylic resonance stabilization at the reacting carbon. For chlorinations involving the more reactive Cl atom the transition state would be even "earlier" in terms of C–H bond breaking, and *presumably* there would be as little or even less rehybridization toward a planar benzylic radical system. We are now ready to apply this model to investigate the *enzymic* functionalization of toluene and related probe molecules.

## Appendix

**$D_0/D_1$ Competition.** As shown in Scheme I the chlorination of a series of mixtures of $D_0$ and $D_1$ (mole fractions $d_0 + d_1 = 1.0$) leads to mixtures of *A* and *B* (mole fractions $a + b = 1.0$), according to eq 1 and 2. Dividing eq 1 by eq 2 gives eq 3, which shows that the product ratio $a/b$ is a linear function (i.e., $y = mx + b$) of the starting material ratio $d_0/d_1$, with slope $m_1$ and intercept $b_1$. From these values one can calculate $P_1$ and $S_1$ directly.

$$a = 3k_{\mathrm{H}}^{\mathrm{HH}}d_0 + k_{\mathrm{D}}^{\mathrm{HH}}d_1 \tag{1}$$

$$b = 2k_{\mathrm{H}}^{\mathrm{HD}} \tag{2}$$

$$a/b = (3k_{\mathrm{H}}^{\mathrm{HH}}/2k_{\mathrm{H}}^{\mathrm{HD}})(d_0/d_1) + k_{\mathrm{D}}^{\mathrm{HH}}/2k_{\mathrm{H}}^{\mathrm{HD}} \tag{3}$$

$$m_1 = 3k_{\mathrm{H}}^{\mathrm{HH}}/2k_{\mathrm{H}}^{\mathrm{HD}} \tag{4}$$

$$b_1 = k_{\mathrm{D}}^{\mathrm{HH}}/2k_{\mathrm{H}}^{\mathrm{HD}} \tag{5}$$

$$S_1 = 2m_1/3 \tag{6}$$

$$P_1 = m_1/3b_1 \tag{7}$$

**$D_1/D_2$ Competition.** To the extent that there is some $D_0$ impurity in $D_1$, this experiment becomes a $D_0/D_1/D_2$ competition. The *A*/*B* and *B*/*C* product mole ratios ($a/b$ and $b/c$, where $a + b + c = 1.0$) are determined from the same set of product analysis data but are processed separately. The $b/a$ ratio is given by eq 10, which is obtained by dividing eq 9 by eq 8 and substituting the definition of $P_1$ (see above). From the slope ($m_{2a}$) and intercept ($b_{2a}$) of eq 10 one can obtained values for $P_2$ and $S_3$ from eq 11 and 12. With the value of $m_1$ from the previous case one can also obtain a second independent estimate of $P_1$ from eq 13.

$$a = k_{\mathrm{D}}^{\mathrm{HH}}d_1 + 3k_{\mathrm{H}}^{\mathrm{HH}}d_0 \tag{8}$$

$$b = 2k_{\mathrm{D}}^{\mathrm{HD}}d_2 + 2k_{\mathrm{H}}^{\mathrm{HD}}d_1 \tag{9}$$

$$(1 + 3P_1d_0/d_1)(b/a) = 2(k_{\mathrm{D}}^{\mathrm{HD}}/k_{\mathrm{D}}^{\mathrm{HH}})(d_2/d_1) + 2k_{\mathrm{H}}^{\mathrm{HD}}/k_{\mathrm{D}}^{\mathrm{HH}} \tag{10}$$

$$P_2 = b_{2a}/m_{2a} \tag{11}$$

$$S_3 = 2/m_{2a} \tag{12}$$

$$P_1 = m_1b_{2a}/3 \tag{13}$$

In a similar fashion the $b/c$ product mole ratio is given by eq 14. From the slope ($m_{2b}$) and intercept ($b_{2b}$) of this equation one obtains a value for $S_2$ (eq 15) and a second independent estimate of $P_2$ (eq 16). With the value of $b_{2a}$ from eq 10, one can also obtain a second independent estimate of $S_3$ (eq 17).

$$b/c = 2(k_{\mathrm{H}}^{\mathrm{HD}}/k_{\mathrm{H}}^{\mathrm{DD}})(d_1/d_0) + 2k_{\mathrm{H}}^{\mathrm{HD}}/k_{\mathrm{H}}^{\mathrm{DD}} \tag{14}$$

$$S_2 = m_{2b}/2 \tag{15}$$

$$P_2 = m_{2b}/b_{2b} \tag{16}$$

$$S_3 = 2m_{2b}/b_{2b}b_{2a} \tag{17}$$

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[16] Russell, G. A.; Brown, H. C. *J. Am. Chem. Soc.* **1955**, *77*, 4031–4035.

[17] Russell, G. A.; Ito, A.; Hendry, D. G. *J. Am. Chem. Soc.* **1963**, *85*, 2976–2983.

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**$D_2/D_3$ Competition.** The product mole ratio $c/b$ is given by eq 20, obtained by dividing eq 18 by eq 19 and substituting the definition of $P_2$ (see above). From the slope ($m_3$) and intercept ($b_3$) of this equation one obtains values for $P_3$ and $S_4$ (eq 21 and 22). With the value of $m_{2b}$ from the case above one can obtain a third independent estimate of $P_2$ (eq 23).

$$c = k_{\mathrm{H}}^{\mathrm{DD}} d_2 + 3k_{\mathrm{D}}^{\mathrm{DD}} d_3 \tag{18}$$

$$b = 2k_{\mathrm{D}}^{\mathrm{HD}} d_2 + 2k_{\mathrm{H}}^{\mathrm{HD}} d_1 \tag{19}$$

$$(1 + P_2 d_1/d_2)(c/b) = (3k_{\mathrm{D}}^{\mathrm{DD}}/2k_{\mathrm{D}}^{\mathrm{HD}})(d_3/d_2) + k_{\mathrm{H}}^{\mathrm{DD}}/2k_{\mathrm{D}}^{\mathrm{HD}} \tag{20}$$

$$P_3 = 3b_3/m_3 \tag{21}$$

$$S_4 = 3/2m_3 \tag{22}$$

$$P_2 = b_3 m_{2b} \tag{23}$$

**$D_0/D_3$ Competition.** If there are small amounts of $D_2$ impurity in $D_3$, product formation under pseudo-first-order conditions will be given by eq 24 and 25, and the product mole ratio $c/a$ will be given by eq 26. The latter is solved by substituting for $k_{\mathrm{H}}^{\mathrm{DD}}/3k_{\mathrm{H}}^{\mathrm{HH}}$ the value $1/3S_1S_2$ (or simply $1/3S^2$) as determined by the foregoing analysis (via. Table II).

$$a = 3k_{\mathrm{H}}^{\mathrm{HH}} d_0 \tag{24}$$

$$c = 3k_{\mathrm{D}}^{\mathrm{DD}} d_3 + k_{\mathrm{H}}^{\mathrm{DD}} d_2 \tag{25}$$

$$\begin{aligned} c/a &= (3k_{\mathrm{D}}^{\mathrm{DD}}/3k_{\mathrm{H}}^{\mathrm{HH}})(d_3/d_0) + (k_{\mathrm{H}}^{\mathrm{DD}}/3k_{\mathrm{H}}^{\mathrm{HH}})(d_2/d_0) \\ &= [k_{\mathrm{D}}^{\mathrm{DD}}/k_{\mathrm{H}}^{\mathrm{HH}} + (k_{\mathrm{H}}^{\mathrm{DD}}/3k_{\mathrm{H}}^{\mathrm{HH}})(d_2/d_3)](d_3/d_0) \end{aligned} \tag{26}$$

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# Amelioration of the Conjugate Addition Chemistry of α-Alkoxycopper Reagents: Application to the Stereospecific Synthesis of *C*-Glycosides

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**Abstract:** ((Benzyloxy)methyl)- and [((tetrahydropyran-2-yl)oxy)methyl]lithium reagents were synthesized via transmetalation of the corresponding α-alkoxystannanes. These lithium reagents were converted into a number of organocopper reagents, and their reactivity with three enones of differing steric demand was examined. The effect of copper(I) precursor as well as additives such as boron trifluoride etherate and chlorotrimethylsilane was examined in detail. Application of this technology to a pair of isomeric tri-*n*-butylstannyl glucopyranosides reveals the scope and limitations for the stereospecific synthesis of *C*-glycosides via conjugate addition reactions to enones.

Despite problems involved in their generation and handling, α-heteroatom substituted lithium reagents have seen extensive application in organic synthesis.[2] Surprisingly, the use of these valuable reagents in copper(I)-mediated conjugate addition reactions has been rare.[3-8] In surveying literature citations related to the general phenomenon of reaction success as a function of copper(I) source purity,[9] we became suspicious that the limited number of applications of (α-alkoxymethyl)cuprates might have been a direct consequence of reagent sensitivity to impurities in the copper(I) source.

As a result of these considerations, it was decided to examine the conjugate addition reactions of several (α-alkoxymethyl)copper reagents. The goal of such experiments was threefold: (1) to determine the sensitivity of these reagents both to handling and copper(I) source purity, (2) to determine the reactivity of these reagents with enones of increasing steric demand, and (3) to minimize the number of equivalents of (α-alkoxymethyl)lithium

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(1) Proctor and Gamble Fellow 1985–1986.

(2) The chemistry of α-alkoxylithium reagents is becoming a relatively mature field, and the preparation of these reagents is possible via transmetalation of α-alkoxystannanes,[2a-g] reductive cleavage of α-alkoxy sulfides,[2h,i] and direct metalation of ethers.[2j,3] (a) Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927. (b) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481. (c) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201. (d) Burke, S. D.; Shearouse, S. A.; Burch, D. J.; Sutton, R. W. *Tetrahedron Lett.* **1980**, *21*, 1285. (e) McGarvey, G. J.; Kimura, M. *J. Org. Chem.* **1982**, *47*, 5422. (f) McGarvey G. J.; Kimura, M. *J. Org. Chem.* **1985**, *50*, 4655. (g) Corey, E. J.; Eckrich, T. M. *Tetrahedron Lett.* **1983**, *24*, 3163. (h) Cohen, T.; Matz, J. R. *J. Am. Chem. Soc.* **1980**, *102*, 6902. (i) Cohen, T.; Lin, M.-T. *J. Am. Chem. Soc.* **1984**, *106*, 1130. (j) Lehmann, R.; Schlosser, M. *Tetrahedron Lett.* **1984**, *25*, 745.

(3) Corey, E. J.; Eckrich, T. M. *Tetrahedron Lett.* **1983**, *24*, 3165.

(4) Eckrich, T. M. Ph.D. Thesis, Harvard University, 1984.

(5) An indirect procedure to produce γ-hydroxy ketones via conjugate addition to enones involves the 1,4 addition of vinylcuprate followed by ozonolysis and selective reduction of the γ-ketoaldehyde: Jones, T. K.; Denmark, S. E. *J. Org. Chem.* **1985**, *50*, 4037. These authors report the specific failure to utilize ((benzyloxy)methyl)cuprate due to formation of the dimerized product, 1,2-bis(benzyloxy)ethane.

(6) Another indirect procedure to achieve the conjugate addition of the α-alkoxymethyl moiety involves reaction of enones with (α-silylmethyl)-cuprates, followed by oxidative insertion to yield the α-siloxymethyl derivative: Tamao, K; Ishida, N. *Tetrahedron Lett* **1984**, *25*, 4249.

(7) There have also been several reports of (*di*alkoxymethyl)cuprate 1,4-addition to enones: (a) Quintard, J.-P.; Elissondo, B.; Pereyre, M. *J. Organomet. Chem.* **1981**, *212*, C31. (b) Shiner, C. S.; Tsunoda, T.; Goodman, B. A.; Lee, S.-H. *Abstracts of Papers*, 192nd National Meeting of the American Chemical Society, Anaheim, CA; American Chemical Society: Washington, DC, 1986; Abstract 227.

(8) After this work was submitted for publication in its original form, a communication appeared concerning α-alkoxycopper reagents: Linderman, R. J.; Godfrey, A. *Tetrahedron Lett.* **1986**, *27*, 4553.

(9) A number of reports have appeared concerning experimental difficulties or outright failure of cuprate reactions as a consequence of poor quality of the copper(I) source: (a) Smith, J. G.; Wikman, R. T. *Synth. React. Inorg. Met.-Org. Chem.* **1974**, *48* 239. (b) House, H. O.; Wilkins, J. M. *J. Org. Chem.* **1978**, *43*, 2443. (c) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841. (d) Iyer, R. S.; Helquist, P. *Org. Synth.* **1985**, *64*, 1. (e) Lipschutz, B. H.; Whitney, S.; Kozlowski, J. A.; Breneman, C. M. *Tetrahedron Lett.* **1986**, *27*, 4273.

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