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Separation of the Primary and Secondary Kinetic Isotope Effects at a Reactive Center Using Starting Material Reactivities. Application to the $FeCl_3$-Catalyzed Oxidation of C-H Bonds with *tert*-Butyl Hydroperoxide

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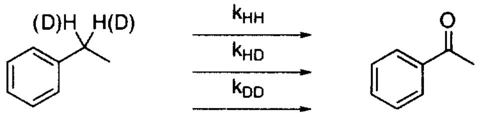
Abstract. A method is reported for the determination of both the primary and secondary kinetic isotope effects at a reactive center based on starting material reactivities. This allows the determination of the separate KIEs in reactions for which neither product analysis nor absolute rate measurements are applicable. The methodology is applied to the $FeCl_3$-catalyzed oxidation of ethylbenzene with tert-butyl hydroperoxide, which exhibits both a primary isotope effect and a substantial secondary isotope effect. © 1999 Elsevier Science Ltd. All rights reserved.

Reactions which break a C-H bond in a methyl or methylene group are subject to two kinetic isotope effects (KIEs), a primary (1°) isotope effect for the C–H bond being broken and a secondary (2°) isotope effect for the C–H bond(s) left behind. Both are mechanistically significant, but the precise determination of both is tricky.[2] The observed isotope effect for reaction of a $-CD_2$ or $-CD_3$ group will be a combination of these two effects. This overall KIE has often been taken as an approximation of the 1° KIE,[3] or else an arbitrary correction for an assumed 2° KIE has been applied.[4] Mechanistic studies interested only in whether a hydrogen transfer is occurring in the rate limiting step can use the overall KIE, as the answer will be apparent if the overall effect is greater than ~2. However, the detailed interpretation of the timing of a transition state or the importance of tunneling in the reaction, or the distinction between hydrogen abstraction and C–H insertion, requires knowledge of both components of the overall isotope effect.

It is possible to separate the KIE components when an isotopic distribution can be measured in the products of a reaction with partially labeled starting material.[5,6] However, measuring isotopic distributions in products is not possible in many reactions, such as oxidation reactions where a second hydrogen is removed from the reactive center after the rate-determining step. Absolute rate differences in unlabeled, mono-deuterated, and di-deuterated starting materials have also been used to separate the isotope effect components.[4b,7] Nevertheless, absolute rate measurements are often insufficiently precise and are impractical for many reactions. Herein we report a general methodology for the determination of both the primary and secondary KIEs at a reactive center from the relative reactivities of starting materials.[8]



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The $FeCl_3$ catalyzed reactions of tert-butyl hydroperoxide with ethylbenzene, 1-deuterioethylbenzene, and 1,1-dideuterioethylbenzene all afford acetophenone as the product. The rates of these reactions will be described as k_{HH}, k_{HD}, and k_{DD}, respectively. With 1-deuterioethylbenzene, k_{HD} will reflect a factor of $1/KIE_{1^\circ}$ if the C-D bond reacts first and a factor of $1/KIE_{2^\circ}$ if the C-H bond reacts first. (KIE_{1° and KIE_{2° are the 1° and 2° k_H/k_D's, respectively.) The overall observed KIE (k_{HH}/k_{HD}) will be given by eq 1, where a statistical factor of 2 is allowed for the two hydrogens in the unlabeled ethylbenzene. With 1,1-dideuterioethylbenzene both the 1° and 2° KIEs will apply and k_{HH}/k_{DD} will be given by equation 2.

$$\frac{k_{HH}}{k_{HD}} = \frac{2}{1/KIE_{1^\circ} + 1/KIE_{2^\circ}} \qquad (1) \qquad\qquad \frac{k_{HH}}{k_{DD}} = KIE_{1^\circ} \times KIE_{2^\circ} \qquad (2)$$

Combining eqs 1 and 2 gives the quadratic equation 3.

$$\left(\frac{k_{HH}}{k_{HD}}\right)(KIE_{1^\circ})^2 - 2\left(\frac{k_{HH}}{k_{DD}}\right)(KIE_{1^\circ}) + \left(\frac{k_{HH}}{k_{HD}}\right)\left(\frac{k_{HH}}{k_{DD}}\right) = 0 \qquad (3)$$

Since eqs 1 and 2 are 'symmetrical' in KIE_{1° and KIE_{2°, a quadratic equation identical to eq 3 would be obtained for KIE_{2°. Assuming that $KIE_{1^\circ} > KIE_{2^\circ}$, KIE_{1° would be the positive root of eq 3 and KIE_{2° would be the negative root, as shown in eqs 4 and 5.

$$KIE_{1^\circ} = \frac{\dfrac{k_{HH}}{k_{DD}} + \sqrt{\dfrac{k_{HH}}{k_{DD}}\left[\dfrac{k_{HH}}{k_{DD}} - \left(\dfrac{k_{HH}}{k_{HD}}\right)^2\right]}}{\dfrac{k_{HH}}{k_{HD}}} \quad (4) \qquad KIE_{2^\circ} = \frac{\dfrac{k_{HH}}{k_{DD}} - \sqrt{\left(\dfrac{k_{HH}}{k_{DD}}\right)\left[\dfrac{k_{HH}}{k_{DD}} - \left(\dfrac{k_{HH}}{k_{HD}}\right)^2\right]}}{\dfrac{k_{HH}}{k_{HD}}} \quad (5)$$

These equations show that the 1° and 2° KIE components can be determined purely from k_{HH}/k_{HD} and k_{HH}/k_{DD}, in principle. However, a subtle but critical difficulty remains – the acquisition of sufficiently precise results for chemical interpretation. The problem arises in the determination of k_{HH}/k_{HD} and the impact of uncertainty in this measurement on KIE_{1° and KIE_{2°. Suppose, for example, that k_{HH}/k_{HD} is measured by ^1H NMR analysis of starting material recovered from a competition reaction of a 1:1 mixture of ethylbenzene and 1-deuterioethylbenzene. The relative integration of methyl and methylene groups would vary only from 1.5:3 at the beginning of the reaction to 1:3 at high conversions with a large k_{HH}/k_{HD}. With a typical k_{HH}/k_{HD} value of ≈ 2 and at an optimum % conversion of $\approx 95\%$, an uncertainty of 3% in the ^1H integration results in an uncertainty of 0.26 in k_{HH}/k_{HD}. This uncertainty in k_{HH}/k_{HD} results in a huge uncertainty in both KIE_{1° and KIE_{2° - $\pm 36\%$ if k_{HH}/k_{DD} is ≈ 5. Obviously KIE_{2° will not be interpretable. The situation is little better in numerous other cases.[9] The successful determination of KIE_{1° and KIE_{2° in the absence of product analysis requires a highly precise determination of k_{HH}/k_{HD}.

This last problem in the measurement of KIE_{1° and KIE_{2° is overcome using the high precision KIEs available at natural abundance by recently reported methodology.[10] In the past this technique has been used to measure 2° deuterium and ^{13}C KIEs, though it would be marginally useful for large primary KIEs.[11] However, the methodology, which takes advantage of an effective competition between all of the possible singly-labeled isotopomers, provides a direct measurement of k_{HH}/k_{HD} for reactions involving equivalent hydrogens.

In the current case, k_{HH}/k_{HD} was determined from the oxidation of natural-abundance ethylbenzene on a 0.5-mole scale in pyridine at 25 °C using 1.2 equiv of tert-butyl hydroperoxide and 5 mol % of $FeCl_3 \bullet 6H_2O$.[12] After allowing the reaction to proceed to 70% completion (144 h), the unreacted ethylbenzene was recovered by an extractive workup followed by distillation, and analyzed by ^{13}C and ^{2}H NMR compared to a standard sample of original ethylbenzene from the same bottle. The changes in ^{13}C and ^{2}H isotopic composition were calculated using the methyl carbon and aryl hydrogens, respectively, as "internal standards" with the assumption that their isotopic composition does not change. (When the ^{2}H spectra were alternatively standardized to the methyl hydrogens the results were the same within experimental error.) From the changes in isotopic composition, k_{12C}/k_{13C} and k_{HH}/k_{HD} were calculated as previously described.[10] The determination of k_{HH}/k_{DD} was carried out using a 45:55 mixture of ethylbenzene and 1,1-dideuteroethylbenzene which was reacted as above to 74% conversion of the ethylbenzene. The ratio of ethylbenzene and 1,1-dideuteroethylbenzene in recovered material was determined by ^{1}H NMR, and k_{HH}/k_{DD} was calculated in a standard fashion. The average results of the various KIE determinations from 6-8 NMR measurements are shown in Table 1, along with $KIE_{1°}$ and $KIE_{2°}$ calculated from eqs 4 and 5.

Table 1. Isotope Effects for the $FeCl_3$-Catalyzed Oxidation of Ethylbenzene with *tert*-Butyl Hydroperoxide

k_{12C}/k_{13C}	k_{HH}/k_{HD}	k_{HH}/k_{DD}	$KIE_{1°}$	$KIE_{2°}$
1.015(2)	2.02(4)	5.0(1)	3.5(2)	1.41(6)

Despite the good precision of the k_{HH}/k_{HD} and k_{HH}/k_{DD} determinations (±2%), the values for $KIE_{1°}$ and $KIE_{2°}$ end up uncertain to ≈±5%. Nonetheless, this is sufficient precision for interpretation. $KIE_{1°}$ is certainly indicative of a C-H bond being broken in the rate limiting step. If $KIE_{1°}$ had just been estimated from k_{HH}/k_{DD} ignoring $KIE_{2°}$, the same conclusion could have been reached (though the value of $KIE_{1°}$ would have been off by >40%). However, $KIE_{1°}$ does not by itself distinguish between a hydrogen radical abstraction and the alternative possibilities of either a C-H insertion or a hydride abstraction. This illustrates the value of also determining $KIE_{2°}$. A C-H insertion reaction would not significantly change the hybridization of the benzylic carbon and $KIE_{2°}$ would be near unity. Rate-limiting hydride abstraction to form a 1-phenylethyl cation would give a $KIE_{2°}$ >1, but the value would be expected to be no greater than about 1.2. Only when the benzylic radical is formed, with the particularly floppy C-H bending modes of carbon radicals, can $KIE_{2°}$ be as large as its observed value.[13] The large value of $KIE_{2°}$ suggests a contribution of tunneling to the KIE, though further experiments would be required to verify this idea.

These results are consistent with current mechanistic understanding of the *tert*-butylhydroperoxide + Fe^{II} or Fe^{III} reactions. Investigations by Minisci[14] and Ingold[15] as well as in these labs[16] have supported the central involvement of *tert*-butoxy or *tert*-butylperoxy radicals in these reactions, and the results here strongly support hydrogen radical abstraction as the key step in the mechanism. Recent studies have shown that *tert*-butylperoxy radicals are generated in reactions employing a co-oxidant to force the Fe^{III}-mediated chemistry, while reactions employing a reductant to force Fe^{II}-mediated chemistry generate *tert*-butoxy radicals.[16b,c] In the absence of an additive *tert*-butoxy radicals mediate the oxidation of cyclohexane via the Fe^{II} chemistry, and this is presumably the case in the reactions of ethylbenzene here. The KIEs observed in this reaction are consistent with those observed in the literature for the reaction of *tert*-butyoxy radicals with toluene (k_{H_3}/k_{D_3} = 4.40 - 6.76 at 130 °C).[3e] Notably, the large $KIE_{2°}$ observed here provides an explanation for the previously puzzling observation that the d_0/d_3 KIE was larger than the 'theoretical maximum' primary KIE at 130 °C.[3e]

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(8) A limitation of KIEs based on starting-material reactivities is that no information is provided about KIEs in product-determining steps after the rate-determining step.

(9) Various possibilities for k_{HH}/k_{HD}, k_{HH}/k_{DD}, % conversion, and starting ratio of labeled and unlabeled material were modeled using an Excel™ spreadsheet. The relative error in $KIE_{1°}$ and $KIE_{2°}$ approaches the relative error in k_{HH}/k_{HD} for very high values of k_{HH}/k_{DD}. Assuming a k_{HH}/k_{DD} of 5 and a maximum practical conversion of 95%, the relative error in $KIE_{1°}$ and $KIE_{2°}$ was never better that ±23%.

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(11) The problem in measuring large isotope effects at high conversion is that small errors in the conversion measurement can lead to large errors in the KIE. Because k_{HH}/k_{HD} will usually be less that ≈2, this methodology can still give reasonably precise measurements.

(12) These reaction conditions are similar to the 'GoAgg^{IV}' 'Gif' oxidation system only with no acetic acid present.

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