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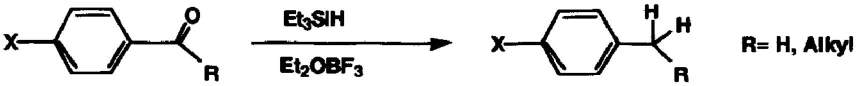
Reductions with Organosilanes. Primary and Secondary Isotope Effects in the Reduction of p-Trifluoromethylacetophenone with Organosilanes.

Ioulia Smonou

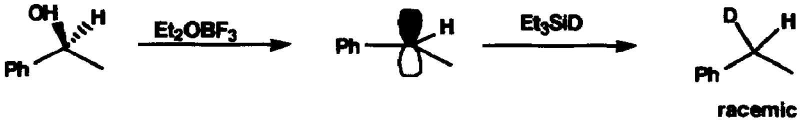
Department of Chemistry, University of Crete, 71110 Iraklion, Crete, Greece

Abstract: The kinetic primary and secondary isotope effects in the reduction of p-trifluoromethylacetophenone with triethylsilane-etherated boron trifluoride were studied.

Organosilanes have been widely recognized as mild and easy to handle reducing agents[1]. Numerous reports have appeared on the reduction of alcohols to hydrocarbons[2] and of aldehydes and ketones either directly to hydrocarbons or to alcohols and ethers, by using triethylsilane in the presence of Brønsted[3] or Lewis acids[4]. We have shown[5] that a system consisting of an organosilicon hydride and etherated boron trifluoride selectively reduces diaryl or alkyl aryl carbinols to hydrocarbons in the presence of other potentially reducible functional groups. By this method we have furthermore reduced aldehydes and ketones to alcohols and hydrocarbons in synthetically useful yields[6].

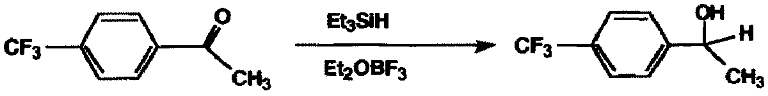


In order to elucidate the mechanism of the alcohol to hydrocarbon transformation, we reported a stereoisotopic study of the reduction of 1-phenylethanol by etherated boron trifluoride-triethylsilane[7]. The absence of a substantial primary kinetic isotope effect and the negligible retention of configuration led us to propose the formation of a cationic intermediate.



We report in this communication some interesting primary and secondary intermolecular kinetic isotope effects in the reduction of ketones to alcohols with triethylsilane in the presence of boron trifluoride that shed some light on the mechanism of the reaction.

We chose for our studies p-trifluoromethylacetophenone because its reduction is slow and gives the alcohol as the final product. not the hydrocarbon.



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To a solution of **1** and a mixture of 1:1 triethylsilane/triethylsilane-d in anhydrous dichloromethane, at 0°C, was added etherated boron trifluoride. Compound **1** was the limiting reagent in a set of three runs with different amounts of 1:1 triethylsilane/triethylsilane-d[7]. The reaction was held under nitrogen, the temperature was left to rise to room temperature, and the progress of the reaction was monitored by VPC analysis. It was complete after 20 hrs. After addition of a saturated solution of sodium carbonate, the organic layer was extracted with ether. The product was isolated in pure form by flash column chromatography (2:1 hexane:ethyl acetate solvent system).

Product ratios were calculated from the integration of the aromatic and methinic proton signals. All NMR analyses were performed on samples which were purified by flash column chromatography. The primary isotope effects, which were measured as a function of reaction progress, are summarized in Table 1.

Table 1 Intermolecular Primary Kinetic Isotope Effects in the Reduction of p-CF_3-$PhCOCH_3$ by $BF_3.Et_2O$-$Et_3SiH(D)$

Entry	p-CF_3-$PhCOCH_3$ mmol	Et_3SiH mmol	Et_3SiD mmol	$k_H/k_D{}^{a,b}$ (RT)
1	0.20	0.50	0.50	1.00 ± 0.05
2	0.30	0.50	0.50	1.00 ± 0.05
3	0.40	0.50	0.50	0.96 ± 0.05

[a]Average of three runs. [b]Determined by integration of the aromatic and methinic hydrogens between 3.5 and 6.5 ppm on Brucker 360MHz and 500MHz NMR spectrometer[8].

In Table 2 are summarized the β-secondary isotope effects in the reaction of 1:1 mixtures of p-CF_3-$PhCOCH_3$/p-CF_3-$PhCOCD_3$ with Et_3SiH in anhydrous dichloromethane. The reactions were run under the same conditions as those reported in Table I. The carbinol products were again separated from the remaining starting ketones with flash column chromatography by using a 2:1 hexane/ethyl acetate solvent mixture. Product ratios were determined by repeated integrations of the methyl and aromatic proton signals.

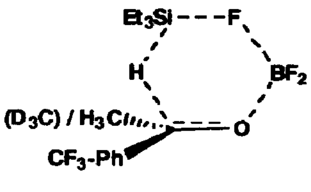
The substantial inverse secondary isotope effect (10%) obtained arises from an increase in the force constants of the carbon-hydrogen vibrations of the -CH_3 (-CD_3) group in going from ground state to transition state. It is consonant with extensive carbon-hydrogen bond making (Si----H(D)-----C) at the transition state, which would reduce the extent of carbon hydrogen hyperconjugation, and/ or a crowded transition state with increased nonbonded interactions. A cyclic transition state, as depicted below, accommodates the available data. It is both more crowded than the ground state, and has reduced C-H(D) hyperconjugative contributions from the methyl group.

Table 2 Intermolecular Secondary Kinetic Isotope Effects in the Reduction of p-CF_3-$PhCOCH_3(CD_3)$ to p-CF_3-$PhCHOHCH_3(CD_3)$ by $BF_3.Et_2O$-Et_3SiH

Entry	p-$CF_3PhCOCH_3$ mmol	p-$CF_3PhCOCD_3$ mmol	Et_3SiH mmol	k_H/k_D[a] (RT)
1	0.50	0.50	0.30	0.89 ± 0.05
2	1	1	1	0.88 ± 0.05

[a]Average of two runs

Quite unexpected was the absence of a primary k_H/k_D effect associated with the transfer of the hydrogen from silicon to carbon. We had anticipated a small normal isotope effect (1.8-2.5) similar to those found in transfers from Si-H to carbocations[9]. However, the structures of those transition states are most likely linear or bent and do not involve extensive carbon-hydrogen bond making[9]. In the present case the transition state is



cyclic, unsymmetrical, and probably involves extensive carbon-hydrogen bond making. It is not unreasonable that in this six-membered cyclic transition state the zero point energy difference associated with the [Si---H(D)-----C] vibrations is comparable to the ground state zero point energy difference of the Si-H(D) vibrations. Although this situation is rarely observed in organic reactions, it may not be unreasonable in the present case. The ground state zero point energy difference of the Si-H(D) vibrations is smaller than that of the corresponding C-H(D) vibrations, because of their weaker force constants. A cyclic and unsymmetrical Si----H(D)-----C transition state with extensive carbon-hydrogen bond making would have substantial contributions to its vibrations from the stronger carbon-hydrogen bond. Therefore, small, or even inverse, primary kinetic isotope effects may not be so rare in such cases.

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