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Kinetic parameters for radical reductions involving chiral nonracemic (1R, 2S, 5R)-menthyl substituted stannanes

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Abstract—Absolute rate constants and Arrhenius parameters for hydrogen atom abstraction by primary alkyl radicals from chiral nonracemic, (1R,2S,5R)-menthyl (Men) substituted stannanes, 1–3, as well as stannanes containing both the menthyl as well as the 8-dimethylaminonaphthyl (L) or 2-[(1S)-1-dimethylaminoethyl]phenyl (L*) substituents, namely MenPhLSnH 4 and MenPhL*SnH 5 have been determined in *tert*-butylbenzene through utilization of the '5-hexenyl radical clock' reaction. At 80 °C, MenPh₂SnH, Men₂PhSnH and Men₃SnH react with primary alkyl radicals with rate constants that fall in the range, $0.61-1.36 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$, while similar values for MenPhLSnH and MenPhL*SnH are 1.30 and $2.74 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ (80 °C), respectively. Arrhenius expressions have been determined for all reactions studied; values for log $(A/M^{-1} \text{ s}^{-1})$ are found to lie in the range: 9.54-9.95, with activation energies determined to be: $15.8-19.7 \text{ kJ} \text{ mol}^{-1}$. Menthyl substitution appears to affect both the energy and entropy of activation. The effect of intramolecular coordination on the rate constants for the reactions involving MenPhLSnH and MenPhL*SnH is discussed and computational data presented.

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1. Introduction

In free-radical chemistry, few reagents have had the same impact as tributyltin hydride.¹⁻³ As a chaincarrying reagent, tributyltin hydride is cheap, readily available, has favourable rate constants for delivery of hydrogen atom to carbon-centred and other radicals⁴⁻¹⁰ while the corresponding stannyl radical reacts readily with a variety of free-radical precursors.¹⁰⁻²³ Formation of carbon-carbon bonds through the use of inter- and intramolecular homolytic addition chemistry, 1-3,24-29 and carbon-heteroatom bonds through the use of homolytic substitution chemistry^{30,31} are key chemical reactions of synthetic significance. The impact of this chemistry has been made possible through significant advances in our understanding of the factors that govern radical reactivity together with a knowledge of the important rate constants involved in the overall chain process.^{1–10}

Recently, we reported the preparation of chiral, nonracemic, (1R,2S,5R)-menthyl (Men) containing stannanes 1–5 for use in enantioselective free-radical reduction chemistry^{32,33} and demonstrated that in conjunction with Lewis acids, these stannanes are capable of providing single enantiomer outcomes for a variety of transformations of synthetic and commercial significance.^{34,35}



An example of this chemistry is shown in Scheme 1, in which (*R*)-naproxen ethyl ester **6** is prepared in 99% enantioselectivity (ee) from racemic bromide **7** by reduction with bis[(1R,2S,5R)-menthyl]phenyltin hydride (Men₂PhSnH) **2** at -78 °C in the presence of magnesium bromide.³⁴





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Given that a knowledge of rate constants is crucial to the design of free-radical reactions of synthetic significance, we have also been determining these important parameters for our recently developed chiral reagents. Herein we report that stannanes **1–5** react with primary alkyl radicals with rate constants that fall in the range, $0.61-2.74 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$, with associated $\log (A/\text{M}^{-1} \text{ s}^{-1})$ and activation energy (kJ mol⁻¹) that lie in the ranges: 9.54-9.95 and 15.8-19.7, respectively. Menthyl substitution appears to affect both energy and entropy terms, while intramolecular coordination in stannanes **4** and **5** activate these stannanes towards homolytic hydrogen transfer.

2. Results and discussion

The menthyl-substituted stannanes used herein were prepared as described previously by us.^{32,33} Absolute rate constants for the delivery of a hydrogen atom to primary alkyl radicals in tert-butylbenzene were determined through application of the well-established '5hexenyl radical clock'³⁶ reaction as described by us.³⁷ An example of the use of the 'clock' as applied to the use of (1R,2S,5R)-menthyldiphenyltin hydride (MenPh₂SnH) 1 is provided in Scheme 2. Provided that the 'clock' rate constant (k_c) is well established for any given temperature, then the rate equation (Scheme 2) will provide a value for the hydrogen transfer rate constant $(k_{\rm H})$. It should be noted that several published Arrhenius parameters exist for the ring closure of the 5-hexenyl radical.^{38–44} Kinetic EPR spectroscopy and competitive experiments provide Arrhenius expressions, with values of 9.5–10.7 for $\log (A/M^{-1} s^{-1})$, and activation energies of 25.5-32.6 kJ mol⁻¹,^{43,44} with the 'best' values being 10.4 ± 0.3 and 28.7 ± 1.8^9 In our previous work,³⁷ we calibrated the 'hexenyl radical clock' in tert-butylbenzene and determined the Arrhenius expression in that solvent to be similar to the expressions determined in other solvents, namely:

$$\log k_{\rm c}/{\rm s}^{-1} = (10.13 \pm 0.42) - (27.6 \pm 2.6)/\theta, \qquad (1)$$

where θ is 2.3*RT* kJ mol⁻¹. We therefore have chosen to use this expression for the 'clock reaction' throughout this work. Reactions of the various stannanes 1–5 with



Table 1. Selected rate constant data (0.10 M) for the reactions of primary alkyl radicals with (1R,2S,5R)-menthyl substituted stannanes 1–5 in *tert*-butylbenzene at 80 °C and comparative data for tributyl-and triphenyltin hydride

Stannane	% 8	% 9	$k_{ m c}/k_{ m H} \ ({ m M})^{ m a}$	$k_{ m H} \ (imes 10^7 \ { m M}^{-1} \ { m s}^{-1})$
Ph ₃ SnH				>1.50 ^b
MenPh ₂ SnH 1	55.2	44.8	12.3	1.36
Men ₂ PhSnH 2	42.7	57.3	7.9	0.82
Men ₃ SnH 3	35.6	64.4	5.5	0.61
Bu ₃ SnH				0.60 ^c
MenPhLSnH 4	47.4	52.6	11.1	1.30
MenPhL*SnH 5	70.0	30.0	22.7	2.50

^a Average of three experiments.

^b Lit.⁴⁵

c Lit.9

1-bromo-5-hexene were initially performed at 80 °C under 'pseudo-first-order' conditions as described in our previous work.³⁷ Selected results of this study are summarized in Table 1 together with available data for tributyl- and triphenyltin hydride.^{45,46}

The remaining kinetic data for reactions at temperatures other than 80 °C were also obtained under 'pseudo-firstorder' conditions. Systematic variations in temperature (60–120 °C) reveal a pleasing linear correlation between log $k_{\rm H}$ and reciprocal temperature. All kinetic data are averages of three experiments and errors in log *A* and activation energy ($E_{\rm a}$) are expressed to 95% confidence and account for random, but not systematic errors. The Arrhenius data obtained in this manner are summarized in Table 2 together with the available data for tributyltin hydride.⁴⁶

Table 2. Kinetic parameters for the reactions of the 5-hexenyl radical with (1R,2S,5R)-menthyl substituted stannanes **1–5** in *tert*-butylbenzene (60–120 °C) and comparative data for tributyltin hydride

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Stannane	$\log A/M^{-1} s^{-1a}$	$E_{\rm a} ({\rm kJ}{\rm mol}^{-1})^{\rm a}$	$k_{\rm H} (80 {}^{\circ}{ m C})^{\rm b} (\times 10^7 { m M}^{-1} { m s}^{-1})$
MenPh ₂ SnH 1	9.95 ± 0.22	19.08 ± 1.52	1.36
Men ₂ PhSnH 2	9.79 ± 0.13	19.52 ± 0.90	0.81
Men ₃ SnH 3	9.70 ± 0.12	19.70 ± 0.84	0.61
Bu ₃ SnH ^c	9.07 ± 0.24	15.45 ± 1.34	0.60
MenPhLSnH 4	9.54 ± 0.33	16.44 ± 2.26	1.30
MenPhL*SnH 5	9.77 ± 0.31	15.80 ± 2.17	2.74

^a Error limits are expressed to 95% confidence but include random and not systematic variations.

^bCalculated from the Arrhenius parameters.

^cRef. 9.

What is immediately clear from the kinetic data presented in Tables 1 and 2 is that the reaction rate constant is largely affected by the number of phenyl substituents on tin, and to a lesser extent by the steric bulk associated with the number of menthyl substituents present. Where intramolecular coordination is possible, stannanes 4 and 5, this phenomenon serves to activate the stannane towards hydrogen transfer; this effect manifests itself in an observed increase in the rate constant. The order of reactivity at 80 °C is clearly $5 > Ph_3SnH > 4 > 1 > 2 > 3 ~ Bu_3SnH$. However, the data in Table 2 suggests that these observations are not solely the result in differences in activation energy (E_a) , but rather the subtle interplay between entropy $(\log A)$ and energy terms. It is clear that the menthyl-substituted stannanes react with $\log A$ values that lie in a narrow range (9.54–9.95) and are very similar within experimental error, but are significantly higher than the value for tributyltin hydride. Despite the similarity in $\log A$ values, the data does indicate a trend: the more menthyl substituents present on tin, the lower (more negative) the entropy of activation becomes.[†] This suggests that the steric influence of the menthyl group is such that it increases E_a , while at the same time providing increasing order to the transition state in the reaction (decreasing $\log A$).

Stannanes 4 and 5, containing potentially intramolecular coordinating ligands on tin, would appear to react significantly more rapidly with primary alkyl radicals than the other stannanes in this study. Indeed, Men-PhL*SnH 5, with a rate constant of $2.74 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$, may even react more rapidly than triphenyltin hydride (> $1.5 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$) at 80 °C. The data presented in Table 2 suggest that intramolecular coordination affects most significantly the activation energies of these two reactions, with log *A* values for 4 and 5, at 9.54 and 9.77, that differ little from those determined for the other menthyl-substituted systems.

It is interesting to compare these data to those reported for reactions of other stannanes with the 5-hexenyl radical. Values of log *A* generally range between 8.8 and 10.0, with activation energies in the range 13– 18 kJ mol^{-1.46} Interestingly, Hershberger and co-workers reported that sterically crowded trimesityltin hydride reacts with the 5-hexenyl radical with a rate constant of $1.1 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$ at 50 °C, and concluded that there is no appreciable steric hindrance restricting the approach of the hexenyl radical to the (supposedly) crowded stannane.⁴⁶ Unfortunately, no Arrhenius parameters are available for this reaction involving the mesityl-substituted stannane.

Apart from being intriguing, this result is in good agreement with those in this current study, namely that the sterically crowded tris[(1R,2S,5R)-menthyl]tin hydride **3** reacts with the 5-hexenyl radical with an almost identical rate constant ($6 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ at 80 °C)

to that of tributyltin hydride at the same temperature. Our Arrhenius data suggests that this outcome may well be entropy driven. As might be expected on steric grounds, **3** has an activation energy some 4.3 kJ higher than Bu₃SnH. However, **3** also has a higher entropy of activation (ΔS^{\dagger}) , which at $-60.6 \text{ J K}^{-1} \text{ mol}^{-1}$ is about $12 \text{ J K}^{-1} \text{ mol}^{-1}$ higher than that determined for Bu₃SnH. These two kinetic parameters operate in a manner that leads to the same rate constant as that of Bu₃SnH at 80 °C. We speculate that a similar phenomenon involving transition state disorder is partly responsible for the reported data involving trimesityltin hydride.

In order to provide further insight into the effect of intramolecular coordination on the stannane reductions in this study, the transition state **11** involved in the transfer of the hydrogen atom from stannane **10** to methyl radical was modeled using the AM1 molecular modeling technique (Scheme 3). This method has been used previously to provide good qualitative transition state data for stannane reductions.^{35,47} The AM1 optimized transition state **11** is displayed in Figure 1 along with that of **12**, calculated for the analogous reaction involving phenylstannane (PhSnH₃) using the same computational technique.

It is worthwhile comparing the AM1 data herein to those from previous work. The calculated transition state distance of about 1.79 Å (C–H) and 1.68 Å (Sn–H) compare favourably with those calculated for other unsubstituted stannanes,⁴⁸ reinforcing our previous observation that substitution at the reacting tin or carbon centres has little influence on the transition state geometry; overall C_{TS} – Sn_{TS} separations are invariably close to 3.5 Å with a preferred co-linear arrangement of attacking and leaving groups.^{35,47}

Interestingly, AM1 would appear to be capable of reproducing the observed activating affect of intramolecular nitrogen coordination. The data presented in Figure 1 clearly indicates that, in good agreement with the experimental data (vide supra), AM1 predicts that nitrogen coordination serves to lower the energy barrier in these hydrogen transfer reactions. Stannane **10** is calculated to react with a methyl radical with a barrier some 3.7 kJ mol⁻¹ lower than the analogous process involving PhSnH₃. In comparison, stannane **5** has been determined to react with the 5-hexenyl radical with an



Scheme 3.

[†] The log *A* values presented in Table 2 translated into entropies of activation (ΔS^{\dagger}) of -55.8, -58.9, -60.6, -72.7, -63.7, -59.3 J K⁻¹ mol⁻¹ in moving down the table from **1** to **5**.



Figure 1. AM1 calculated transition states 11 (left) and 12 (right).

energy barrier about 3.3 kJ mol⁻¹ lower than the uncoordinated analogue 1.

3. Computational chemistry

AM1 calculations were performed within Gaussian 98.49 Geometry optimizations were performed using standard gradient techniques and vibrational frequencies were calculated on each calculated structure.

4. Experimental

Typical kinetic experiment. An aliquot $(100 \,\mu\text{L})$ of a standard solution (0.05-0.15 M) of the stannane in tertbutylbenzene was placed in a small pyrex tube, 1-bromo-5-hexene (ca. 0.1 equiv) and AIBN (ca. 1 crystal) were added and the solution degassed by the usual freeze-thaw technique, before being sealed under vacuum. After being thermolyzed in an oil bath at the required temperature the solution was analyzed by GC.

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