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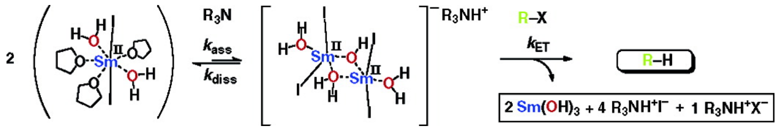
J. Am. Chem. Soc., **2005**, 127 (23), 8340-8347• DOI: 10.1021/ja043323u • Publication Date (Web): 14 May 2005



Journal of the American Chemical Society is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

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Published on Web 05/14/2005

Mechanistic Study of the SmI_2/H_2O/Amine-Mediated Reduction of Alkyl Halides: Amine Base Strength (pK_{BH+}) Dependent Rate

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Abstract: The kinetics of the SmI_2/H_2O/amine-mediated reduction of 1-chlorodecane has been studied in detail. The rate of reaction is first order in amine and 1-chlorodecane, second order in SmI_2, and zero order in H_2O. Initial rate studies of more than 20 different amines show a correlation between the base strength (pK_{BH+}) of the amine and the logarithm of the observed initial rate, in agreement with Brønsted catalysis rate law. To obtain the activation parameters, the rate constant for the reduction was determined at different temperatures (0 to +40 °C, $\Delta H^{\ddagger} = 32.4 \pm 0.8$ kJ mol^{-1}, $\Delta S^{\ddagger} = -148 \pm 1$ J K^{-1} mol^{-1}, and $\Delta G^{\ddagger}_{298K} = 76.4 \pm 1.2$ kJ mol^{-1}). Additionally, the ^{13}C kinetic isotope effects (KIE) were determined for the reduction of 1-iododecane and 1-bromodecane. Primary ^{13}C KIEs (k_{12}/k_{13}, 20 °C) of 1.037 ± 0.007 and 1.062 ± 0.015, respectively, were determined for these reductions. This shows that cleavage of the carbon−halide bond occurs in the rate-determining step. A mechanism of the SmI_2/H_2O/amine-mediated reduction of alkyl halides is proposed on the basis of these results.

Introduction

Reduction reactions represent a class of reactions that is central in organic synthesis, where mainly three types of reagents are used: hydride reagents, hydrogen, and dissolving metals.[1] Today there are already a vast number of different reagents and methods available for the reduction of, for example, alkyl halides to hydrocarbons. However, the development of new more efficient and selective methods, using environmentally friendly reagents and possibly nonexplosive hydride/hydrogen-based compounds, constitutes an important task for the organic chemist. In this respect the single electron transfer reagent SmI_2 has received much interest since it has been found to promote a number of selective reductions and reductive couplings.[2] Alkyl halides are readily and often with high selectivity reduced into hydrocarbons by SmI_2.[3] However, SmI_2 is not a very potent reducing reagent by itself; often it is used in combination with the carcinogenic compound hexamethylphosphortriamide (HMPA), since the reduction potential of SmI_2/HMPA is considerably higher compared to that of SmI_2.[4] There are a few potential nontoxic substitutes to HMPA, but none of these have received much attention.[5]

Recently, we discovered that addition of H_2O and an aliphatic amine to SmI_2 in THF results in a very powerful reductant (SmI_2/H_2O/amine). SmI_2/H_2O/amine is a much more powerful reductant than the commonly used SmI_2−HMPA mixture. The rate enhancement in the reduction of ketones is more than 100 000 times that without the amine (or approximately 1000 times compared to SmI_2−HMPA−MeOH), i.e., practically instantaneous.[6] During our continuing study we have observed that the SmI_2/H_2O/amine mixture also reduces imines, α,β-unsaturated esters, halides, and conjugated double and triple bonds.[7,8] Additionally, SmI_2/H_2O/amine readily cleaves allyl-protected alcohols.[9] The reagent mixture SmI_2/H_2O/amine is particularly attractive not only because of its fast reductions but also since it is a nonhazardous reducing agent.

To fully appreciate and develop new reactions using the reagent mixture SmI_2/H_2O/amine, it is important that details

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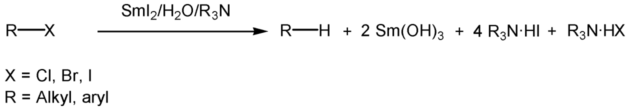

Figure 1. Reduction of alkyl halides by SmI_2/H_2O/amine.

regarding its mechanism of reduction are better understood. SmI_2 is suggested to be a monomer in THF, and it crystallizes as a pentagonal bipyramid, i.e., $SmI_2(THF)_5$.[10] Furthermore, we and other groups have previously shown that addition of water to a THF solution of SmI_2 results in a significant shift of the visible band,[7,11] indicating that one or several water molecules replace THF ligands around samarium, i.e., $SmI_2(H_2O)_n(THF)_{5-n}$. The amine appears to increase the oxidation potential of SmI_2, but no such effect has been established experimentally, suggesting that the driving force for the reduction may be the precipitation of the byproducts, $Sm(OH)_3$ and $R_3NH^+I^-$. However, the choice of amine affects the rate of reduction, which indicates that the amine must be intimately involved in the reduction mechanism.

The complete reduction of 1.0 mol of alkyl iodide requires 2.0 mol of SmI_2, 5.0 mol of amine, and 6.0 mol of water. This stoichiometry has been explained on the basis of the formation of $Sm(OH)_3$ and R_3NHX salts that are observed to precipitate out of the solution (Figure 1).[7]

It is known that secondary halides are reduced faster than primary halides. Additionally, it is clear that the leaving group properties of the halides affect the rates of reduction, i.e., I > Br > Cl. No primary kinetic isotope effect, i.e., $k_{H_2O}/k_{D_2O} = 1.0$, was found for these reactions.[7]

Herein, we report the results on extensive kinetic studies of the SmI_2/H_2O/amine-mediated reductions of simple alkyl halides along with the dependence of the basicity of the amine versus the rate of reduction. The temperature dependence of the rate constant and the kinetic isotope effect for the reduction of 1-chlorodecane and 1-bromodecane have also been determined. Based on the results of these studies a mechanism for the SmI_2/H_2O/amine-mediated reduction reaction of alkyl halides is suggested.

Results

Kinetics. The method of initial rates can be used for precise and convenient determination of the reaction orders in a complex system, as long as the reaction follows the same kinetics throughout the course of the reaction.[12] The first-order kinetics in alkyl halide (R−X) was verified by following the SmI_2/H_2O/amine-mediated reduction of different alkyl halides to at least 50% conversion and plotting $\ln([R-X]_t/[R-X]_0)$ versus time. This yielded a straight line with the slope equal to $-k_{obs}$ (Supporting Information).

1-Chlorodecane was chosen as substrate for the detailed kinetic studies since it reacts at a rate that allows accurate determination of the initial rate. First, the kinetics of the background reduction of 1-chlorodecane by SmI_2 in THF with and without H_2O added was studied. Reaction rates were measured by monitoring the formation of decane, in small quenched portions of the reaction mixture, by GC. By individually varying the component concentrations over at least an 8-fold range the reaction order in each component was obtained from the slope of the plots of log(initial rate) vs log[component]. The reaction order with respect to both SmI_2 and halide was determined to obtain the rate equation, eq 1. The rate of reduction by SmI_2 was found to be first order with respect to both SmI_2 and 1-chlorodecane. With H_2O added a first-order dependence was found for all three components, eq 2.

$$\text{rate} = v_{\text{initial}} = k_{\text{obs}}[\text{SmI}_2][\text{1-chlorodecane}] \qquad (1)$$

$$\text{rate} = v_{\text{initial}} = k_{\text{obs}}[\text{SmI}_2][\text{1-chlorodecane}][\text{H}_2\text{O}] \qquad (2)$$

The reaction orders of the reduction of 1-chlorodecane were then determined in the presence of SmI_2/H_2O/amine, Figure 2. The respective reaction order for each component of the reaction mixture is given in Table 1.

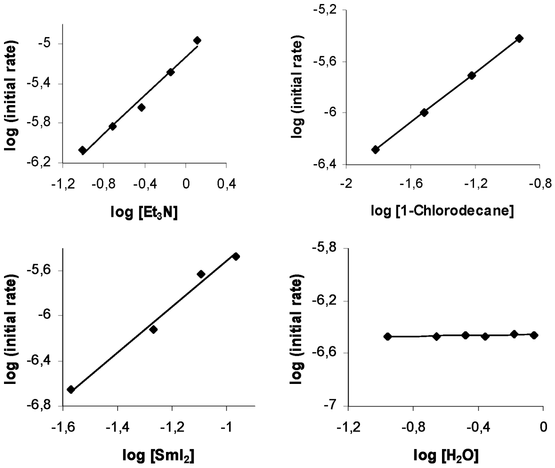

Figure 2. Plots of log(initial rate) vs (a) log[Et_3N], (b) log[1-chlorodecane], (c) log[SmI_2], and (d) log[H_2O].

Table 1. Determined Reaction Orders with Respect to the Respective Components of the $SmI_2/H_2O/R_3N$-Mediated Reduction of 1-Chlorodecane

component	reaction order[a]
SmI_2	2.0 ± 0.1
H_2O	0.1 ± 0.1
1-chlorodecane	0.96 ± 0.04
triethylamine	0.98 ± 0.03
TMEDA	1.0 ± 0.1
PMDTA	0.95 ± 0.03 (at 1 equiv PMDTA)[b]
pyrrolidine	0.99 ± 0.1

[a] The reported maximum errors are obtained from two separate experiments. [b] The reaction order was 0.00 ± 0.03 when [PMDTA] < [SmI_2].

The reaction orders in the reduction of 1-chlorodecane with a mixture of SmI_2, H_2O, and an aliphatic amine (Et_3N, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDTA), or pyrrolidine) were found to be first order in halide and amine, zero order in H_2O, and second order in SmI_2, eq 3.

$$\text{rate} = v_{\text{initial}} = k_{\text{obs}}[\text{SmI}_2]^2[\text{1-chlorodecane}][\text{amine}] \quad (3)$$

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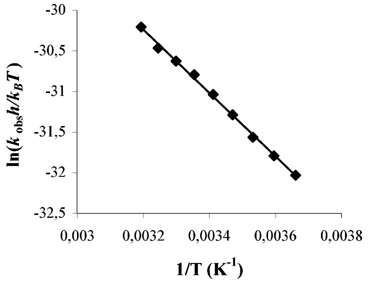

Figure 3. Eyring plot obtained by plotting $\ln(k_{obs}h/k_BT)$ vs $1/T$.

Interestingly, the reaction order in PMDTA is zero at low concentrations ([PMDTA] < [SmI_2]). This is probably due to the coordination of one PMDTA to one SmI_2; however at higher PMDTA concentrations the reaction is first order in PMDTA, similarly to the other amines.

We also determined relative rates for reduction of the different alkyl halides (I, Br, Cl). The relative rates for the reduction of 1-iododecane, 1-bromodecane, and 1-chlorodecane were approximately 1200:50:1. From the relative initial rates it was found that the activation energy (based on $\Delta G^\ddagger = -\ln(k_{rel}h/k_BT)$) is approximately 7.9 kJ mol^{-1} higher for the reduction of bromodecane and 18 kJ mol^{-1} higher for 1-chlorodecane compared to that of 1-iododecane.

It is known that the reduction of primary (1-chlorodecane), secondary (*s*-BuCl), and tertiary (*t*-BuCl) alkyl chlorides varies along the series according to $k_{prim} < k_{sec} < k_{tert}$, indicating that the number of alkyl substituents of the halide carbon has an effect on the relative rate of reduction. In accordance with the method by Rieke and co-workers, we determined the relative rates of reduction of primary, secondary, and tertiary alkyl chlorides.[13] The rate of reduction of 1-chlorodecane relative to *s*-BuCl and *t*-BuCl was determined under pseudo-first-order rate conditions (assuming similar rates of reduction of *n*-BuCl and 1-chlorodecane). In these measurements 1 equiv of SmI_2, 3 equiv of H_2O, 4 equiv of Et_3N, 10 equiv of 1-chlorodecane, and 10 equiv of *s*-BuCl or *t*-BuCl were used. The reaction mixtures were analyzed with GC (with respect to 1-chlorodecane) when all SmI_2 had been consumed, i.e., when the color of SmI_2 had fully vanished. The relative rates, obtained in these competition experiments, revealed that *s*-BuCl and *t*-BuCl reacted 2 and 15 times faster, respectively, than 1-chlorodecane.

Temperature Dependence. The temperature dependence of the reduction of 1-chlorodecane with $SmI_2/H_2O/Et_3N$ was studied over the temperature interval from 0 to 40 °C with increments of 5 °C. The measured initial rate is related to k_{obs} according to the obtained rate expression for the reaction (eq 3),[14] with the assumption that the concentration of each component is approximately equal to their initial concentration (pseudo-first-order rate condition). An Eyring plot was obtained by plotting $\ln(k_{obs}h/k_BT)$ vs $1/T$ (Figure 3).

Activation parameters for the reduction reaction were obtained from the linear correlation according to the Eyring equation ($\ln(k_{obs}h/k_BT) = -\Delta H^\ddagger/RT + \Delta S^\ddagger/R$), i.e., $\Delta H^\ddagger = 32.4 \pm 0.8$ kJ mol^{-1}, $\Delta S^\ddagger = -148 \pm 1$ J K^{-1} mol^{-1}, and $\Delta G^\ddagger_{298} = 76.4 \pm 1.2$ kJ mol^{-1}. The corresponding Gibbs free energy of activation was calculated from $\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$ at 298 K.

Amine Basicity. During the kinetic studies it was observed that the rate of reduction was strongly dependent on the choice of amine. The reductions appeared to be fastest with secondary amines and slowest with tertiary amines, i.e., approximately related to the basicity of the alkyl amines, tertiary < primary < secondary. Initial rates of reduction were determined for a large number of substituted alkyl amines at 20 °C (Table 2). The basicity corresponds to the pK_{BH+} values of the amines in water (estimated with the ACD software).[15,16]

Table 2. Determined Initial Rate ($v_{initial}$)[a] of Reduction for the Respective Amines with the Estimated pK_{BH+}[b]

entry	amine	$v_{initial}/\mu M\ s^{-1}$	pK_{BH+}
1	tribenzylamine	0.05	6.9 ± 0.5
2	*N*-methylmorpholine	0.09	7.4 ± 0.1
3	TMEDA	0.70	8.6 ± 0.1
4	2-methoxyethylamine	1.17	8.8 ± 0.1
5	morpholine	1.22	9.0 ± 0.2
6	benzylamine	2.51	9.4 ± 0.1
7	PMDTA	4.12	9.6 ± 0.4
8	tributylamine	0.45	10.0 ± 0.5
9	*N*-methylpyrrolidine	1.99	10.6 ± 0.2
10	cyclohexylamine	20.9	10.6 ± 0.1
11	triethylamine	2.87	10.6 ± 0.3
12	isopropylamine	17.3	10.7 ± 0.3
13	*n*-butylamine	26.2	10.7 ± 0.1
14	diethylamine	26.7	10.8 ± 0.1
15	diisopropylamine	25.9	10.8 ± 0.3
16	*N*-ethyldiisopropylamine	2.04	11.0 ± 0.3
17	*n*-dibutylamine	13.6	11.0 ± 0.2
18	*N*-cyclohexylisopropylamine	14.4	11.0 ± 0.2
19	quinuclidine	36.7	11.1 ± 0.1
20	piperidine	29.8	11.2 ± 0.2
21	pyrrolidine	59.2	11.3 ± 0.2
22	2-methylpiperidine	20.0	11.3 ± 0.4
23	2,6-dimethylpiperidine	19.0	11.4 ± 0.6
24	dicyclohexylamine	54.7	11.4 ± 0.2
25	hexamethyldisilazane	0.44	14.4 ± 0.7

[a] [SmI_2] = 0.11 M, [Et_3N] = 0.11 M, [H_2O] = 0.33 M, and [1-chlorodecane] = 0.016 M. [b] The pK_{BH+} are obtained from ACD lab.[15]

The use of less basic aryl amines, e.g., substituted pyridines, together with SmI_2 and H_2O in the reduction of 1-chlorodecane failed. The characteristic blue color of SmI_2 in THF disappeared immediately, indicating that Sm^{2+} was oxidized to Sm^{3+}. No trace of the reduced alkyl halide could be detected after workup. This indicates that these less basic aryl amines are reduced to piperidines in the reaction mixture, which Kamochi and Kudo have reported previously.[17]

Addition of the very basic amine hexamethyldisilazane, HMDS ($pK_{BH+} = 14.4$), to SmI_2/H_2O did not increase the rate of reduction. in fact this rate was slightly lowered compared to the rate of SmI_2/H_2O alone. The reaction orders were also determined for each of the components of the mixture SmI_2/H_2O/HMDS. The expression for the initial rate was identical to that of the SmI_2 in THF-mediated reduction (eq 1) when [HMDS] > [H_2O]. The lack of rate enhancement using

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(14) k_{obs} is obtained by dividing the initial rate with $[SmI_2]^2[R-X][amine]$.

(15) ACD Lab, ACD/pK_a, DB 1996−2004, Advanced Chemistry Development. The pK_a predictions are based on 16 000 compounds and 30 000 experimental pK_a values. Additionally, the pK_a prediction algorithm applies a linear free energy relationship (Hammett equation) and sigma constants to describe the level of electron donation and withdrawal at the ionization center. Correction for organic solvent can also be applied.

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the strong base HMDS could indicate that it is too basic to be used together with water.

A surprisingly good correlation was obtained in the Brønsted plot constructed by plotting the initial rates of reduction vs the pK_{BH+} of the corresponding protonated amines, BH^+ (Figure 4). Only the hindered, tertiary amines, such as Bu_3N and $Et(i\text{-}Pr)_2N$, are slightly outside the linear correlation, possibly due to some steric effects. From the slope of the plot of $\log(\upsilon_{initial})$ vs pK_{BH+} a Brønsted value of 0.60 was estimated (Figure 4b). Exclusion of the values for tertiary amines certainly gives a better correlation; however the Brønsted β is only affected slightly (~0.64), concluding that a higher pK_{BH+} of the amines give higher rates of reduction.

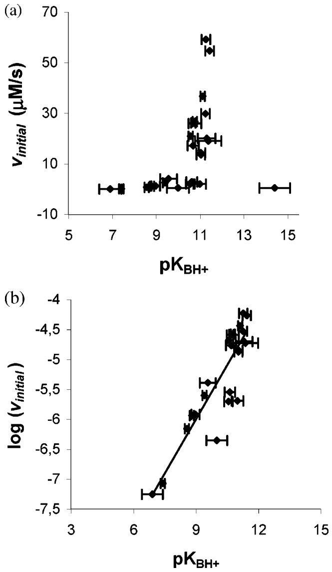

Figure 4. (a) Plot of initial rate ($\upsilon_{initial}$) vs pK_{BH+} and (b) $\log(\upsilon_{initial})$ vs pK_{BH+} of the protonated amines. The result for HMDS has been excluded in the linear plot, as it is protonated by water.

UV Studies. Water is known to coordinate to SmI_2 in THF, giving rise to a characteristic UV band indicating that H_2O replaces THF in the coordination sphere of SmI_2, Figure 5. Careful inspection of the UV bands shows that there are three isosbestic points present, at 407, 474, and 521 nm, respectively.

Addition of the strong amine HMDS to a solution of SmI_2 and H_2O results in a UV spectrum identical to that of pure SmI_2 in THF. This indicates that neither HMDS nor water is coordinated to SmI_2. HMDS most likely deprotonates water, resulting in an ion-pair ($HMDSH^+OH^-$), which precipitate out of the THF solution. Addition of any of the other amines in Table 2 to a mixture of SmI_2/H_2O in THF did not affect the UV spectra.

Comparison of Nucleophilicity. The dependence of the initial rate with choice of amine can also indicate that the amines act as nucleophiles since the nucleophilicity of amines generally correlates well with their basicity. To exclude the possibility that the reaction does not involve nucleophilic catalysis, triethyl phosphine (Et_3P), which is a known powerful nucleophile and a weak base, was utilized. Interestingly, the rate of reduction using $SmI_2/H_2O/Et_3P$ was lower than that with only SmI_2/H_2O, and the rate of reduction decreased with increasing amounts of Et_3P.

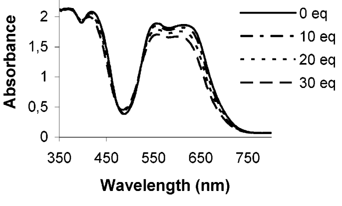

Figure 5. UV spectra of SmI_2 in THF with increasing amounts of H_2O added.

It is also possible that the free iodide (I^-) could act as a catalyst for the reduction reactions. Iodide is a known good nucleophile; therefore the kinetics of the SmI_2/H_2O/amine-mediated reduction of 1-chlorodecane was also studied in the presence of excess LiI (3:1 molar ratio of LiI:SmI_2). However, no measurable difference in initial rates was observed. Catalytic amounts of HgI_2 and NiI_2 are other additions that previously have been reported to accelerate some SmI_2-mediated reactions,[18] but neither HgI_2 nor NiI_2 could be used in the SmI_2/H_2O/amine-mediated reduction of alkyl halides. They were instantaneously reduced to Hg(0) and Ni(0), in agreement with their low reduction potentials.

Additions of NaOH, NH_4Cl, or LiCl. To probe if the reduction of 1-chlorodecane is faster at higher pH, the reduction was carried out after addition of saturated aqueous NaOH (50%) with a 1:2 molar ratio of NaOH−SmI_2. Interestingly, the reduction of the alkyl halide by $SmI_2/NaOH/H_2O$ proceeded with an initial rate approximately 15 times as high as that using SmI_2/H_2O alone. However, the large rate enhancements were only observed for a few percent of the reaction, and at about 5% conversion the reaction had almost stopped, possibly due to breakdown of SmI_2.

Addition of 3 equiv of NH_4Cl to a mixture of H_2O and SmI_2 resulted in a small increase in the rate of reduction of 1-chlorodecane. The rate of the $SmI_2/NH_4Cl/H_2O$-mediated reduction was determined to be 2.5 times faster than that by SmI_2/H_2O. Furthermore, a small enhanced rate of reduction upon addition of LiCl to SmI_2/H_2O was also observed. This small but significant increase in rate is in agreement with an observation, reported by Flowers et al., that LiCl increases the reduction potential and the reactivity of SmI_2.[19]

Kinetic Isotope Effects. Kinetic isotope effects (KIEs) are useful in mechanistic studies, as they can give information about rehybridization changes occurring in the transition state. The size of a primary heavy ^{13}C KIE in the $SmI_2/H_2O/Et_3N$-mediated reduction of alkyl halides could also indicate that the rate-determining step involves the breakage of the carbon−halogen bond. Likewise there should also be a secondary kinetic isotope effect if there is a rehybridization of the CH_2 bonded to the halide. Accurate ^{13}C or ^2H KIE can be obtained from the change in isotopic composition ($^{13}C/^{12}C$) of reactions taken to 85−95% conversion using a simple method extensively used by, for example, Singleton.[20] The analysis requires only ^{13}C or ^2H NMR integrals of reference materials and unreacted reactants. The KIE is calculated from eqs 4 and 5 below, where the term (R/R_0) is

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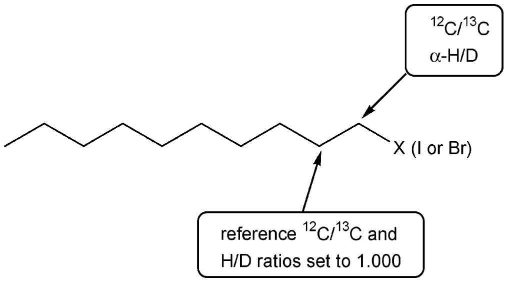


Figure 6. ^{13}C KIEs were obtained from the isotopic ratios ($^{12}C/^{13}C$) and H/D for the C1-methylene group of 1-iododecane and 1-bromodecane in the reduction by $SmI_2/H_2O/Et_3N$ in THF. The isotopic ratio of the C2-methylene group is used as internal reference (assumed 1.000).

Table 3. Observed KIEs for the Reduction of 1-Iodododecane and 1-Bromodecane Mediated by $SmI_2/H_2O/Et_3N$ in THF

alkyl halide	conversion (%)	isotopic ratio	KIE
1-iododecane	96	1.134	1.037 ± 0.007 (k_{12}/k_{13})
1-bromodecane	85	1.117	1.062 ± 0.015 (k_{12}/k_{13})
		1.086	1.041 ± 0.020 (k_H/k_D)

the proportion of minor isotopic component in recovered material compared to the original starting material and the variable (F) is the fractional conversion of reactant.

$$R/R_0 = (1 - F)^{(1/\mathrm{KIE})-1} \tag{4}$$

$$\mathrm{KIE}_{\mathrm{calcd}} = \frac{\ln(1 - F)}{\ln[(1 - F)R/R_0]} \tag{5}$$

Since 1-chlorodecane is slowly reduced with $SmI_2/H_2O/Et_3N$ and quantitative yields are difficult to obtain, 1-iododecane and 1-bromodecane were instead employed in these heavy atom KIE studies. The relative change of the ^{13}C integral of the C1-carbon vs the C2-carbon (used as internal standard) corresponds to the relative change in the isotopic composition of ^{13}C at the C1 carbon, Figure 6. The C2 carbon integral was used as internal standard since it does not participate in the reaction; hence its isotopic composition is unaffected by the reaction conditions. The primary ^{13}C KIE (k_{12}/k_{13}) for the cleavage of the carbon−iodide bond was found to be 1.037 ± 0.007 at 20 °C.

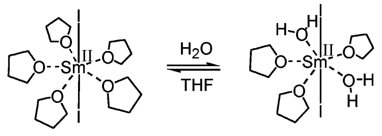
1-Bromodecane was treated with $SmI_2/H_2O/Et_3N$, and the reaction was taken to 85% conversion. The ^{13}C kinetic isotope effect for the C1 carbon was calculated from the fractional conversion and the measured changes in isotopic composition. The primary ^{13}C KIE (k_{12}/k_{13}) for the cleavage of the carbon−bromide bond was 1.062 ± 0.015 at 20 °C. Natural abundance ^2H NMR was employed to obtain the $^1H/^2H$ isotopic composition of the remaining 1-bromodecane compared to a reference sample of unreacted 1-bromodecane. The secondary k_H/k_D KIE was determined to be 1.041 ± 0.020. In these KIE studies no compensation for contributions from isotope effects imposed by the halide was made, simply because the effects would be too small to be observed by the method used.[21]

Discussion

Dimerization of SmI_2 by Amine and Water. SmI_2 exists as a pentagonal bipyramid, $SmI_2(THF)_5$, in THF.[10] The isosbestic points in the UV−vis spectra indicate that H_2O replaces one or several THF molecules in $SmI_2(THF)_5$, e.g., $SmI_2(H_2O)_n(THF)_{5-n}$, to form *one* new complex (Scheme 1). Previously we have reported on the absence of an observable change of the UV−vis spectra for the SmI_2−THF solution upon addition of aliphatic monodentate amines (having $pK_{BH+} < 13$); that is, it does not coordinate to the SmI_2 complex in the initial state.[7]

Addition of the tridentate amine N,N,N',N'',N''-pentamethyldiethylene triamine (PMDTA) results in a shift of the UV−vis, yielding several isosbestic points. Thus, the tridentate amine PMDTA competes effectively with THF in coordination to SmI_2. On the basis of the isosbestic points in the UV−vis spectrum, it is suggested that there is only one PMDTA coordinated to SmI_2 in the initial state.[22] This also establishes that the amine is not strong enough to deprotonate $SmI_2(H_2O)_n(THF)_5$ to any significant extent, as judged from the UV−vis spectra, although we cannot exclude a possible dimerization of SmI_2 induced by H_2O.

Scheme 1



A

Recently Flowers and co-workers reported that water coordinates much stronger to SmI_2 than alcohols.[11] In addition they found that water gives the highest rate enhancement in the reduction of acetophenone, indicating that water may be unique among proton donors to promote dimerization. However, the rate of reduction is zero order in water and first order in amine, regardless of the amine used (Et_3N, TMEDA, PMDTA, or pyrrolidine), despite the fact that these amines differ largely in both structure and basicity. This indicates similar reaction mechanisms. The kinetic zero order with respect to water suggests that it binds tightly to SmI_2 in THF. Assuming that SmI_2 is a monomer in the initial state, then a second-order dependence on SmI_2 shows that the transition state is a dimer or that the reaction proceeds in two steps with the second being rate determining. The background reductions of the alkyl halide (by SmI_2 or SmI_2/H_2O) proceed via significantly different mechanisms than SmI_2/H_2O/amine. The reduction reaction using SmI_2/H_2O is first order in SmI_2, H_2O, and alkyl halide.

Electron Transfer from SmI_2 to the Alkyl Halide. Water is crucial for the fast reaction by SmI_2/H_2O/amine but does not appear in the rate expression because it is coordinated to SmI_2 in the initial state. The amine is not coordinated to SmI_2 in the initial state, but it could be part of a rapid and unfavorable acid−base pre-equilibrium leading to a short-lived dimeric high-energy intermediate. Moreover, the reduction of 1-chlorodecane by SmI_2/H_2O/amine proceeds with a small enthalpy and large negative entropy of activation. The negative entropy of activation indicates that there are more molecules bound in the transition state than in the initial state. The enthalpy of activation of 32.4 kJ mol^{-1} is almost identical to the value of 33 kJ mol^{-1} reported by Flowers et al. for the reduction of 1-iodobutane by a SmI_2−HMPA mixture.[23] However, the entropy of activation

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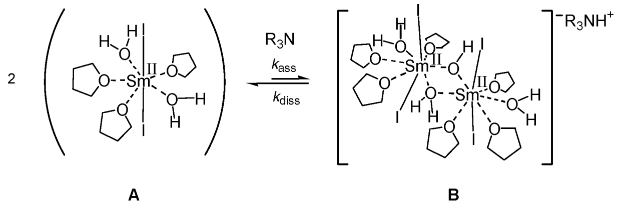
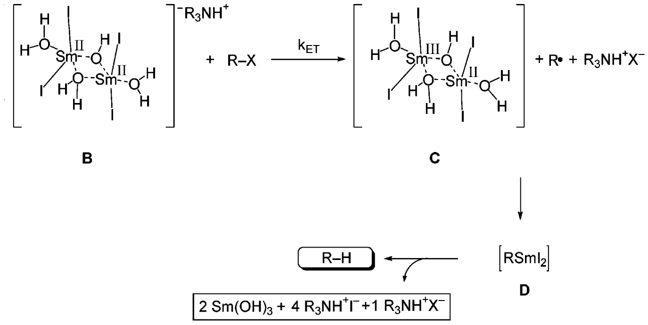
(21) Values of approximately 1.003 and 1.010 have been reported in the literature for $^{79}Br/^{81}Br$ and $^{35}Cl/^{37}Cl$ KIE, respectively. (a) Dybaa-Defratyka, A.; Rostkowski, M.; Matsson, M.; Westaway, K. C.; Paneth, P. *J. Org. Chem.* **2004**, *69*, 4900−4905. (b) Lewandowicz, A.; Sicinska, D.; Rudzinski, J.; Ichiyama, S.; Kurihara, T.; Esaki, N.; Paneth, P. *J. Am. Chem. Soc.* **2001**, *123*, 9192−9193.

(22) The equilibrium constant of SmI_2 + PMDTA $\overset{K}{\rightleftharpoons}$ SmI_2(PMDTA) was determined from the UV spectra, $K = 33\ \mathrm{M}^{-1}$, see ref 7.

Scheme 2



Scheme 3. Mechanism Describing the Final Steps in the Reduction of Alkyl Halides (solvent molecules have been excluded for clarity)



of −148 J K^{-1} mol^{-1} for SmI_2/H_2O/amine is significantly more negative than the value of −125 J K^{-1} mol^{-1} for SmI_2−HMPA. This substantial loss in entropy indicates that the reaction proceeds through a larger molecular assembly, possibly a dimer (Scheme 2).

Altogether, the results of the kinetic measurements indicate that the amine is involved in an unfavorable, fast deprotonation of a coordinated water molecule in complex **A**. The absence of changes in the UV−vis spectra with the addition of an amine to complex **A** indicates a necessary, but also unfavorable, pre-equilibrium deprotonation that transforms into the short-lived anion intermediate **B**.

Complex **B**, being negatively charged, can be the powerful reductant responsible for the fast reductions with SmI_2/H_2O/amine. Thus, the activated complex for the SmI_2/H_2O/amine-mediated reduction of 1-chlorodecane is suggested to consist of a dimer of SmI_2 with one bridging water molecule, one hydroxide, and possibly two more coordinated water molecules, the protonated amine, and the alkyl halide, Scheme 3. It is possible that dimers of SmI_2 with bridging water molecules may also exist in the absence of amine.[24] Corresponding bridging oxygens bound to two samariums have previously been observed for Sm^{III} in the solid state.[25] The occurrence of dimeric samarium species has also been proposed by Curran et al. to explain the mechanistic behavior of intramolecular samarium Barbier couplings.[26]

Inner vs Outer Sphere Electron Transfer. The observed ^{13}C kinetic isotope effects (k_{12}/k_{13}) of 1.037 ± 0.007 and 1.062 ± 0.015 for 1-iododecane and 1-bromodecane, respectively, indicate partial carbon−halide bond breakage in the rate-determining step, in agreement with the proposed mechanism. The heavy atom KIE is slightly larger with 1-bromodecane than with 1-iododecane, as expected from their differences in mass.[27]

The electron transfer (ET) from complex **B** to the alkyl halide may proceed via an inner or an outer sphere mechanism. The k_{12}/k_{13} KIE does not differ significantly for an inner and an outer sphere electron transfer mechanism.[28] On the other hand the secondary-deuterium KIEs have been suggested to differ considerably for electron transfer mechanisms proceeding via outer sphere ($k_H/k_D \approx 1.01-1.04$) and inner sphere electron transfer ($k_H/k_D \approx 1.30-1.50$). The observed small secondary k_H/k_D KIE of 1.041 ± 0.020 therefore suggests that the reduction of 1-bromodecane proceeds via an outer sphere electron transfer mechanism. However, the validity of this distinction has been questioned since some electron transfers may be diffusion controlled.[29] There are also different opinions whether the SmI_2/HMPA-mediated reduction of alkyl halides proceeds through an inner or an outer sphere electron transfer.[23,30] Still, the clean reaction orders strongly indicate a system with an unstable intermediate. Therefore the rate of electron transfer is much lower than that of dissociation of the SmI_2 precomplex **B**, i.e., $k_{ET} \ll k_{diss}$ (Schemes 2 and 3). The Marcus theory describes outer sphere electron transfer reactions.[31] According to this theory outer sphere ET generally shows a correlation between $\Delta G^\ddagger$ and ΔG° for the reaction. The $\Delta G^\ddagger$'s for the reduction of the decyl halides were obtained from the respective initial rates, and the ΔG°'s for the alkyl halides were taken from the potentials of butyl chloride ($E = 1.246$ V), butyl bromide ($E = 1.105$ V), and butyl iodide ($E = 1.075$ V) reported by Savéant and co-workers (assuming similar relative potentials for decyl and butyl).[32] The experiments show that decyl bromide and decyl chloride have 7.9 and 18 kJ mol^{-1}, respectively, higher activation energy than decyl iodide, while the reported free energies are 3.3 and 18 kJ mol^{-1}, respectively, higher than decyl iodide. Thus, there is indeed a good correlation between $\Delta G^\ddagger$ (decyl halides) and ΔG° (butyl halides) with the slope being almost unity, consistent with an outer sphere electron transfer.

The outer sphere electron transfer to alkyl halides has received much attention; both Savéant and Fukuzumi with co-workers have reported that the rate of reduction is insensitive to steric hindrance.[32,33] Furthermore, Rieke and co-workers reported that there is only a limited difference in rate of reductions of isomeric alkyl halides for outer sphere electron transfer reactions.[13] An alkyl halide that undergoes outer sphere ET has $\ln(k_{s-R-X}/$

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(28) Holm and Crossland have reported a $k_{12}/k_{13} = 1.035$ for inner sphere electron transfer to CH_3I to generate methyl radicals at 250 °C. They estimated that the k_{12}/k_{13} would correspond to 1.056 at 20 °C. They also reported that an outer sphere electron transfer mechanism may give rise to a k_{12}/k_{13} KIE of 1.023 ± 0.009. Holm T.; Crossland I. *Acta Chem. Scand.* **1996**, *50*, 90−93.

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k_{n-R-X}) of less than unity and $\ln(k_{t-R-X}/k_{n-R-X})$ less than 3, respectively. By taking the logarithm of the relative rate ratios, it was found that $\ln(k_{s-BuCl}/k_{1-chlorodecane}) = 0.6$ and $\ln(k_{t-BuCl}/k_{1-chlorodecane}) = 2.7$, indicating that the reduction by $SmI_2/H_2O/$amine mainly proceeds through an outer sphere process.

Amine Base Strength Dependent Rate. The observed Brønsted β of 0.6 may indicate significant proton transfer in the activated complex; however in the absence of an observable KIE ($k_{H_2O}/k_{D_2O} = 1.0$) the proton transfer cannot be involved in the rate-determining step.[7] The role of the amine may thus be to deprotonate a water molecule coordinated to SmI_2 in a pre-equilibrium. The proton transfer is therefore suggested to occur in such a fast pre-equilibrium leading to a high-energy intermediate, occurring prior to the actual electron transfer step. In such a model there should be only an equilibrium isotope effect, which would be close to unity.[34] The observed Brønsted β thus indicates that a stronger base is able to push the equilibrium toward the high-energy intermediate, with a faster overall rate of reduction. Water molecules coordinated to a Lewis acid, i.e., samarium diiodide, should show an enhanced acidity; that is, the pK_a of Lewis acid coordinated water molecules is approximately 9.[35]

The use of Brønsted β values in mechanistic studies is somewhat controversial, and there are different interpretations of what a certain value indicates.[36] The Brønsted β value may reflect the charge formed in the transition state rather than the extent of bond formation. It should also be emphasized that these reductions proceed in mixtures of THF$-H_2O$ (37:1) and not in pure H_2O, for which the Brønsted catalysis law is defined. The β value can also be a measure of the nucleophilicity of the amine, suggesting that an amine coordinated to SmI_2 could result in a more powerful reductant. However, previous cyclic voltammetric (CV) studies on the SmI_2(PMDTA) complex have shown that this complex is not a stronger reducing agent than $SmI_2(THF)_5$, and the use of the powerful nucleophile Et_3P did not result in enhanced reaction rates of reduction. This proves that the large rate enhancements found with the amines are due to their *basicity* and not their nucleophilicity.

The strong base HMDS did not accelerate the reduction rate despite its higher pK_{BH+} value. This could be due to its higher basic strength that allows it to deprotonate water, thus removing the coordinated water from SmI_2, and thereby the high reactivity of SmI_2 is lost. The result is that $SmI_2(THF)_5$ is regenerated, and this compound is not a powerful reductant, Scheme 4.

Scheme 4

$$SmI_2(THF)_5 + n\,H_2O \underset{THF}{\overset{K_1}{\rightleftharpoons}} SmI_2(THF)_{5-n}(H_2O)_n$$

$$SmI_2(THF)_{5-n}(H_2O)_n + HMDS \underset{THF}{\overset{K_2}{\rightleftharpoons}} SmI_2(THF)_5 + HMDSH^+OH^-$$

The low number of reductive couplings that have been observed using the $SmI_2/H_2O/$amine mixture indicates that free radicals are reduced faster than they dimerize or undergo various coupling reactions. We have observed reductive coupling reactions only between aromatic ketones and imines and the *intra*molecular aryl halide olefin coupling.[8a,c,37] This is probably due to the fact that these generated radicals are relatively stable and long-lived.

Fast electron transfer to the radical from the remaining Sm^{II} in the mixed Sm^{II}/Sm^{III} dimer complex is suggested to result in an organosamarium(III) complex, which rapidly decomposes in the presence of H_2O and the amine. Such organosamarium intermediates are assumed to be central in the SmI_2-mediated reduction of alkyl halides.[38] Breakdown of the organosamarium intermediate into R$-$H must proceed after the rate-limiting step. Once the stable byproducts $Sm(OH)_3$ and $R_3NH^+X^-$ are formed, they precipitate from the solution.

The above mechanism suggests that the use of $NaOH/H_2O$ instead of amine/H_2O would lead to a similar mechanism. However, the initially fast reduction (ca. 15 times faster) using $SmI_2/NaOH/H_2O$ is observed only for a fraction of the reaction, after which the rate of reduction is slow and similar to that of SmI_2/H_2O. This is probably due to rapid breakdown of SmI_2 in this harsh environment and because the driving force from precipitated ammonium salts is lost when no amine is present. Addition of other salts (NaI, LiI, NaCl, or NH_4Cl) has no significant effect on the rate of reduction, although the sodium and lithium salts have limited solubility in THF. The addition of excess NH_4Cl (3 equiv) results in a 2.5 times increase in the rate of reduction by SmI_2/H_2O. This small, but significant, increase in rate is in agreement with Flowers finding that LiCl increases the reduction potential and the reactivity of SmI_2.[19] This effect is similar to that observed by the addition of LiBr. Thus, the presence of the ammonium ion NH_4^+ is not a prerequisite for the fast reduction reaction.

Conclusion

During the studies of the mechanism we encountered that the rate of reduction of 1-chlorodecane was strongly dependent on the basicity of the amine. Although the correlation is somewhat scattered, the stronger bases clearly give higher rates. Aryl amines and amines with pK_{BH+} below 9 are not capable of accelerating the SmI_2/H_2O-mediated reduction. A maximum in the rate constant is observed with aliphatic amines having pK_{BH+} in the range of 10.7 to 11.4. The more basic amine HMDS (with a pK_{BH+} of 14.4) are ineffective in promoting this reduction. It has been shown that very strongly basic amines such as HMDS are protonated by the added water.

The rate of the $SmI_2/H_2O/$amine-mediated reduction of 1-chlorodecane is first order in amine and 1-chlorodecane, second order in SmI_2, and zero order in H_2O. From the studies of ^{13}C KIE and the reaction orders we propose that the reduction of alkyl halides by $SmI_2/H_2O/$amine proceeds via a rate-determining electron transfer from a dimeric $SmI_2(H_2O)$ intermediate to the halide. This intermediate is suggested to result from a general base-catalyzed deprotonation of SmI_2-coordinated water. The large negative entropy of activation (-148 J K^{-1} mol^{-1}) gives further indication that a large molecular assembly occurs in the transition state. The ET appears to proceed mainly

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(34) Equation 3 could therefore also be expressed as rate $= v_{initial} = k'K_{eq}[SmI_2]^2$-[1-chlorodecane][amine], where $k_{obs} = k'K_{eq}$.

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via an outer sphere mechanism. Daasbjerg and co-workers have reported that the SmI_2/HMPA reduction of alkyl halides proceeds via both inner and outer sphere ET and that the outer sphere character decreases with increasing atom number (Cl > Br > I).[30b]

Preliminary results from our laboratory have shown that the basicity of the amine used in the reagent mixture SmI_2/H_2O/amine also affects the rate of reduction of conjugated olefines, pinacol couplings, imino-pinacol couplings, intramolecular cyclization reactions, and allyl ether clevages. The amine dependence of the reactivity of the SmI_2/H_2O/amine reagent may allow differences in selectivity when dealing with polyfunctional substrates. Currently we are investigating if the choice of amine also affects the selectivity in competing reactions such as reduction vs coupling reactions.

Experimental Section

General Procedures. THF was distilled from sodium and benzophenone under nitrogen atmosphere. The amines were distilled under nitrogen atmosphere and stored over molecular sieves. SmI_2, additives, and solvents were stored under nitrogen atmosphere in a glovebox containing typically less than 1 ppm H_2O and O_2, respectively.

Reductions of Alkyl Halides. In a standard initial rate measurement, SmI_2 in THF (0.11 M, 7 equiv) was added to a dry Schlenk tube, fitted with a septum, and containing a magnetic stirrer bar, inside a glovebox with nitrogen atmosphere. Dodecane was added to the tube, as internal standard for the GC analysis. The amine (14 equiv) and the proton donor, i.e., H_2O (21 equiv), were added at 20.0 °C. Rate measurements were obtained by following each reaction from approximately 1% to 5% conversion. For the Eyring plot the reaction mixtures were equilibrated at the given temperature for 15 min before the alkyl halide (1 equiv) was added slowly using a gastight syringe. Throughout these studies a thermostatic bath with a temperature stability of 0.5 °C was employed. Small portions of the mixture (200 μL) were removed via a syringe and quenched with I_2 in *n*-hexane (0.1 M, 0.1 mL). To the quenched solution were added diethyl ether (1 mL) and HCl (0.12 M, 0.1 mL) to dissolve the inorganic salts and finally $Na_2S_2O_3$ to remove excess iodine. The organic layer was transferred to a vial, and the yield of decane was analyzed with GC. An internal standard (dodecane) was used to obtain the rate constants.

Gas Chromatography. The progress of the reaction was monitored using a GC fitted with an achiral stationary phase column ($\phi = 0.25$ mm, length = 25 m), using hydrogen as carrier gas at a flow rate of 2 mL/min and a initial column temperature of 50 °C. The injector temperature was 225 °C. The detector temperature was 250 °C (FID). The products were identified using authentic samples.

UV−Vis Measurements. All UV−vis spectra were recorded on a UV−vis−NIR spectrophotometer connected to a computer. The SmI_2 solutions were diluted to 3.6 mM inside a glovebox in a quartz cuvette equipped with a screwcap fitted with a septum. The path length of the cuvette was 1.00 cm. Successive additions of the additives were made with a gastight syringe through the septum, and a new spectrum was recorded after each addition.

KIE Studies. The reduction of 1-iododecane and 1-bromodecane to decane mediated by $SmI_2/H_2O/Et_3N$ in THF on a 31.6 mmol scale at 20 °C was taken to 96% and 85% conversion, respectively. Two sets of NMR (700 μL of $CDCl_3$ in 5 mm NMR tubes) samples were prepared, one obtained from the partial conversion of the alkyl halide (ca. 100 mg of 1-iodododecane or 700 mg of 1-bromodecane), isolated after extraction and distillation under reduced pressure, and the corresponding reference samples of 1-iododecane and 1-bromodecane, not subjected to the reaction conditions. The ^{13}C spectra were obtained at 125.703 MHz with a custom built ^1H,^{13}C,^6Li probe (Nalorac) on a 500 MHz NMR spectrometer (Varian Unity500). NMR experiments with ^1H decoupling and NOE as well as experiments with inverse gated ^1H decoupling were collected separately to obtain relative integrals with identical results within experimental error. We used calibrated 90° pulses and >5 T_1 delays (for the slowest decaying peak of interest) between pulses (30 s for 1-iododecane) and a 4.99 s acquisition time to collect 128 000 data points. The signal-to-noise-ratios were 700−1000. A zero-order baseline correction was applied for the integrals, and the integrations were determined numerically using a constant integration region for each peak of the references 1-iodododecane and 1-bromodecane and the recovered unreacted alkyl halide samples, respectively.

The ^2H spectra were obtained at 76.736 MHz with broadband probe (Nalorac) on a 500 MHz NMR spectrometer (Varian Unity500). NMR experiments with ^1H decoupling and NOE as well as experiments with inverse gated ^1H decoupling were collected separately to obtain relative integrals with identical results within experimental results. We used calibrated 90° pulses and >5 T_1 delays (for the slowest decaying peak of interest) between pulses (30 s for 1-iododecane) and a 4.99 s acquisition time to collect 128 000 data points. The signal-to-noise-ratios were better than 200:1. A zero-order baseline correction was applied for the integrals, and the integrations were determined numerically using a constant integration region for each peak of the reference 1-bromodecane and the recovered unreacted 1-bromodecane samples, respectively.

Acknowledgment. Mr. Roine I. Olsson is gratefully acknowledged for the estimation of the pK_{BH+} values using the ACD-Lab software. Prof. Robert Flowers, II and Dr. Edamana Prasad (Lehigh University), Dr. Sten Nilsson Lill (Göteborg University), and Prof. Vernon Parker (Utah State University, Logan) are gratefully acknowledged for helpful discussions. Financial support from the Carl Trygger Foundation and the National Science Council (Vetenskapsrådet) is also thankfully acknowledged.

Supporting Information Available: This material is available free of charge via the Internet at http://pubs.acs.org.

JA043323U