Notes

Debrominations of *vic*-Dibromides with Diorganotellurides. 3. Rate Constants, Eyring and Arrhenius Activation Parameters, and Mechanistic Implications

Timothy S. Butcher and Michael R. Detty*

Department of Medicinal Chemistry, School of Pharmacy,
SUNY at Buffalo, Amherst, New York 14260, and
Department of Chemistry, SUNY at Buffalo,
Amherst, New York 14260

Received February 23, 1999

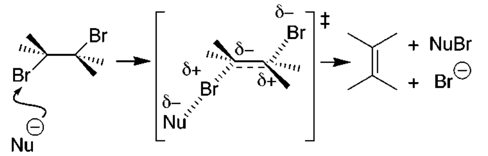
Introduction

The dehalogenation of *vic*-dihalides to generate olefins has been accomplished with a variety of reagents.[1−4] Although these reactions are in many ways redundant (the *vic*-dihalide is typically generated from the corresponding olefin), the combination of stereospecific halogenation of an olefin and subsequent stereospecific dehalogenation of the resulting *vic*-dihalide offers a means of protection for the carbon−carbon double bond in synthesis.

To utilize these reactions more effectively for specific protection/deprotection sequences, an understanding of structure/activity relationships in both dehalogenating agent and dihalide substrate would be desirable. Stereospecific debrominations with nucleophilic reagents such as iodide[2] or 2-thienyltelluride[3d] have been proposed to occur through the E2-like process depicted in Scheme 1. In this model, synchronous loss of bromide and formation of the carbon−carbon double bond accompany nucleophilic attack at one bromine. However, few mechanistic details for the reactions of either iodide or 2-thienyltelluride with *vic*-dibromides are available to support this mechanism unequivocally.

We have demonstrated that diaryl- and dialkyltellurides also give highly stereoselective debrominations of *vic*-dibromides with a variety of substitution patterns even though these reagents are less nucleophilic than iodide and 2-thienyltelluride.[4] Reactivity patterns are quite different in comparisons of iodide and dihexyltelluride (**1**) with selected substrates and suggest that more than one mechanism may be involved in debrominations of *vic*-dibromides with nucleophilic debrominating agents.[4a] In this paper, we address some of the mechanistic issues through the temperature-dependent kinetics of debromination of *vic*-dibromides with either dihexyltelluride (**1**) or Bu_4NI.

Scheme 1



Scheme 2

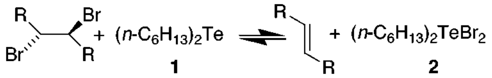


Table 1. Initial Reaction Velocities (v_{init}) for Olefin Formation from the Reaction of *vic*-Dibromides with Dihexyltelluride (1) or Bu_4NI at (338 ± 1) K in $CDCl_3$ at Various Concentrations of Reagents

Substrate	Debrominating Reagent	M[a]	v_{init},[b] M s^{-1}	v_{rel}
3	$Te(n\text{-}C_6H_{13})_2$	0.40	$(3.1 \pm 0.1) \times 10^{-8}$	16
	1	0.20	$(7.6 \pm 0.1) \times 10^{-9}$	4.0
		0.10	$(1.9 \pm 0.2) \times 10^{-9}$	1
3	$n\text{-}Bu_4NI$	0.40	$(7.0 \pm 0.4) \times 10^{-6}$	15
		0.20	$(1.7 \pm 0.1) \times 10^{-6}$	3.7
		0.10	$(4.6 \pm 0.1) \times 10^{-7}$	1
4	$Te(n\text{-}C_6H_{13})_2$	0.40	$(4.1 \pm 0.1) \times 10^{-6}$	18
	1	0.20	$(1.1 \pm 0.1) \times 10^{-6}$	4.8
		0.10	$(2.3 \pm 0.1) \times 10^{-7}$	1
4	$n\text{-}Bu_4NI$	0.40	$(8.1 \pm 0.2) \times 10^{-5}$	16
		0.20	$(2.3 \pm 0.1) \times 10^{-5}$	4.5
		0.10	$(5.1 \pm 0.1) \times 10^{-6}$	1

[a] Concentration of both *vic*-dibromide and debrominating agent.
[b] Average of duplicate runs

Results and Discussion

Reaction Order. Earlier studies have shown that the debrominations with **1** are reversible processes.[4a,5] If one assumes that the debrominations are second-order processes as illustrated in Scheme 2, then the reaction can be drawn with the *vic*-dibromide and **1** on one side of the equilibrium and the olefin and dihexyltellurium dibromide (**2**) on the other.

Debrominations of 1,2-dibromodecane (**3**) and 2,3-dibromo-2-methylpentane (**4**) with equimolar concentra-

---

(1) With zinc and magnesium: Baciocchi, E. In *Chemistry of Functional Groups, Supplement D, Part 1*; Patai, S., Rappoport, H., Eds.; Wiley: New York, 1983.

(2) With iodide: (a) Plattner, P. A.; Heusser, H.; Segre, H. *Helv. Chim. Acta* **1948**, *31*, 249. (b) Solo, A. J.; Singh, B. *J. Org. Chem.* **1965**, *30*, 1658.

(3) With tellurium reagents: (a) Campos, M. d. M.; Petragnani, N.; Thomé, C. *Tetrahedron Lett.* **1960**, (15), 5−8. (b) Campos, M. M.; Petragnani, N. *Chem. Ber.* **1961**, *94*, 1759. (c) Ramasamy, K.; Kalyanasundarani, S. K.; Shammugan, P. *Synthesis* **1978**, 311. (d) Engman, L. *Tetrahedron Lett.* **1982**, *23*, 3601. (e) Suzuki, H.; Inouye, M. *Chem. Lett.* **1985**, 225. (f) Huang, X.; Hou, Yu Q. *Synth. Commun.* **1988**, *18*, 2201. (g) Li, C. J.; Harpp, D. N. *Tetrahedron Lett.* **1990**, *31*, 6291. (h) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574. (i) Barton, D. H. R.; Bohe, L.; Lusinchi, X. *Tetrahedron Lett.* **1987**, *28*, 6609. (j) Desilva, K. G. K.; Monsef-Mirzai, Z.; McWhinnie, W. R. *J. Chem. Soc., Dalton Trans.* **1983**, 2143.

(4) (a) Butcher, T. S.; Zhou, F.; Detty, M. R. *J. Org. Chem.* **1998**, *63*, 169. (b) Butcher, T. S.; Detty, M. R. *J. Org. Chem.* **1998**, *63*, 177.

(5) Leonard, K. A.; Zhou, F.; Detty, M. R. *Organometallics* **1996**, *15*, 4285.

10.1021/jo990332q CCC: $18.00

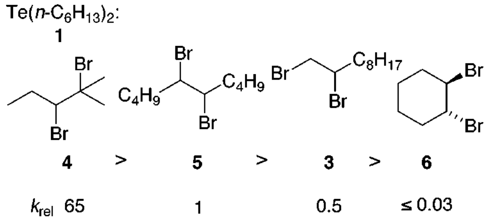
Table 2. Rate Constants ($k \pm 2\sigma$) for the Debromination of 1,2-Dibromodecane (3), 2,3-Dibromo-2-methylpentane (4), *erythro*-5,6-Dibromodecane (5), and *trans*-1,2-Dibromocyclohexane (6) with Either Dihexyltelluride (1) or Bu_4NI at 338 K

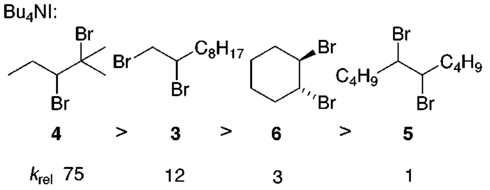
Substrate	Debrominating Reagent	$k \pm 2\sigma$, M^{-1} s^{-1}	k_{rel}
3	$Te(n\text{-}C_6H_{13})_2$	$(1.93 \pm 0.07) \times 10^{-7}$	1
	Bu_4NI	$(4.45 \pm 0.07) \times 10^{-5}$	230
4	$Te(n\text{-}C_6H_{13})_2$	$(2.49 \pm 0.05) \times 10^{-5}$	130
	Bu_4NI	$(5.0 \pm 0.2) \times 10^{-4}$	1500
5	$Te(n\text{-}C_6H_{13})_2$	$(3.85 \pm 0.05) \times 10^{-6}$	2
	Bu_4NI	$(3.9 \pm 0.2) \times 10^{-7}$	20
6	$Te(n\text{-}C_6H_{13})_2$	$< 1.0 \times 10^{-8}$	≤ 0.05
	Bu_4NI	$(1.06 \pm 0.09) \times 10^{-5}$	55

tions of either telluride **1** or Bu_4NI in $CDCl_3$ were followed by ^1H NMR spectroscopy. Since analysis of the kinetics of debromination with **1** will be complicated by the equilibrium depicted in Scheme 2, reaction orders were determined from initial reaction velocities with both **1** and Bu_4NI (Table 1). The observed ratios for 0.4, 0.2, and 0.1 M concentrations of reagents are close to the 16:4:1 ratios expected for a second-order process overall and suggest that these reactions are first order in both substrate and debrominating agent.

Relative Rates of Reaction. The relative rates of debromination of 1,2-dibromodecane (**3**), 2,3-dibromo-2-methylpentane (**4**), *erythro*-5,6-dibromodecane (**5**), and *trans*-1,2-dibromocyclohexane (**6**) were determined with both telluride **1** and iodide as debrominating agent. The kinetics of debromination were evaluated under pseudo-first-order conditions to avoid complications from the equilibrium depicted in Scheme 2.[4a] Second-order rate constants for these systems with both telluride **1** and Bu_4NI were measured with either telluride or iodide in excess (0.20−0.80 M) of the dibromide concentration of 0.025 M in $CDCl_3$ at 338 K. The progress of reaction was followed by ^1H NMR spectroscopy. The second-order rate constants compiled in Table 2 were derived from a plot of the observed pseudo-first-order rate constants for debromination as a function of telluride or iodide concentration. The debromination of *trans*-1,2-dibromocyclohexane (**6**) with telluride **1** was not readily resolved from an uncatalyzed, thermal debromination, and the rate constant in Table 2 represents an upper limit for telluride-induced debromination. Relatives rates of reactivity with each reagent are shown below.

For each of the substrates **3**−**6**, iodide was more reactive than telluride **1** as a debrominating agent (Table 2). However, the relative rates of debromination within the series **3**−**6** were quite different with telluride **1** or Bu_4NI as shown above. For both reagents, 2,3-dibromo-2-methylpentane (**4**) was the most reactive substrate and was roughly 70-fold more reactive than *erythro*-5,6-dibromodecane (**5**). Striking differences were noted in the rates of debromination of 1,2-dibromodecane (**3**) and *trans*-1,2-dibromocyclohexane (**6**). While **6** was essentially unreactive in debrominations with telluride **1** (≤0.03 of the reactivity of **5**), **6** was 3-fold more reactive than **5** in debrominations with Bu_4NI. 1,2-Dibromodecane (**3**) was 12-fold more reactive than **5** with Bu_4NI as debrominating agent but was half as reactive as **5** with telluride **1** as debrominating agent.





The order of reactivity observed for substrates **3**−**6** with telluride **1** as debrominating agent (**4** > **5** > **3** > **6**) is that expected if carbocation/bromonium ion character is developed in the transition state: increased branching in the dibromide leads to faster rates of reaction.[4a] Other studies have shown that strain impacts bromonium ion stability and that bicyclic bromonium ions such as the bromonium ion derived from **6** are less favored relative to bromonium ions derived from acylic substrates, which is consistent with the lower reactivity of **6** with telluride **1**.[6] With Bu_4NI as debrominating agent, **4** is also the most reactive substrate and is also roughly 70-fold more reactive than **5**. However, 1,2-dibromodecane (**3**) is 12-fold more reactive than **5** as one might expect for the E2-like process depicted in Scheme 1. The differences in reactivity with **1** and Bu_4NI suggest that at least two mechanistic paths are being followed in these processes.

Activation Parameters and Possible Mechanisms of Reaction. As one probe of mechanism, Eyring and Arrhenius activation parameters were determined for selected substrates with both telluride **1** and Bu_4NI as debrominating agents. For the *vic*-dibromides **3**−**6**, substrate **3** would offer the least steric hindrance to nucleophilic attack of the debrominating agent while substrate **4** would be most likely in this series to form carbocation or bromonium ion intermediates. One would expect differences in the associated activation parameters of reaction if different mechanistic paths were followed. Second-order rate constants for debrominations of **3** and **4** were measured in $CDCl_3$ with either telluride or iodide in excess at several concentrations (0.20, 0.40, 0.60, and 0.80 M) of the dibromide concentration of 0.025 M over the temperature range 338−368 K. Second-order rate constants are compiled in Table 3 along with the Eyring and Arrhenius activation parameters determined from the plots of Figures 1 and 2.

For 1,2-dibromodecane (**3**), values of E_a, ln A, $\Delta G^{\ddagger}_{298}$, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ were identical within experimental error for debrominations with either telluride **1** or with iodide (Table 3) and suggest mechanistically related reactions with these debrominating agents. The mechanism pro-

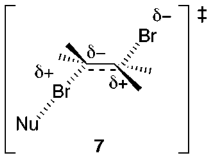
---

[6] (a) Olah, G. *Halonium Ions*; Wiley: New York, 1975; Chapter 7. (b) Olah, G. A.; Bollinger, J. M.; Brinich, J. *J. Am. Chem. Soc.* **1968**, *90*, 2587. (c) Olah, G. A.; Schilling, P.; Westerman, P. W.; Lin, H. C. *J. Am. Chem. Soc.* **1974**, *96*, 3581.

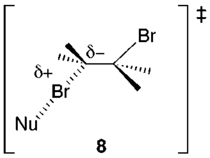
Table 3. Temperature-Dependent, Second-Order Rate Constants ($k \pm 2\sigma$) for the Debromination of 1,2-Dibromodecane (3) and 2,3-Dibromo-2-methylpentane (4) with Either Dihexyltelluride (1) or Bu4NI and Associated Eyring and Arrhenius Activation Parameters

Substrate	Debrominating Reagent	T (±1), K	$k \pm 2\sigma$, M^{-1} s^{-1}	Eyring and Arrhenius Activation Parameters (± 2σ)
3	$Te(n\text{-}C_6H_{13})_2$ **1**	338 348 358 368	$(1.93 \pm 0.07) \times 10^{-7}$ $(4.5 \pm 0.2) \times 10^{-7}$ $(1.36 \pm 0.09) \times 10^{-6}$ $(2.65 \pm 0.08) \times 10^{-6}$	$\Delta G^{\ddagger}_{298}$ = 29 ± 5 kcal mol^{-1} $\Delta H^{\ddagger}$ = 22 ± 3 kcal mol^{-1} $\Delta S^{\ddagger}$ = −26 ± 9 cal mol^{-1} K^{-1} E_a = 22 ± 3 kcal $mole^{-1}$ ln A = 18 ± 5
3	$n\text{-}Bu_4NI$	338 348 358 368	$(4.45 \pm 0.09) \times 10^{-5}$ $(9.4 \pm 0.2) \times 10^{-5}$ $(2.66 \pm 0.07) \times 10^{-4}$ $(4.8 \pm 0.1) \times 10^{-4}$	$\Delta G^{\ddagger}_{298}$ = 26 ± 5 kcal mol^{-1} $\Delta H^{\ddagger}$ = 20 ± 3 kcal mol^{-1} $\Delta S^{\ddagger}$ = −21 ± 8 cal mol^{-1} K^{-1} E_a = 20 ± 3 kcal $mole^{-1}$ ln A = 20 ± 4
4	$Te(n\text{-}C_6H_{13})_2$ **1**	338 348 358 368	$(2.49 \pm 0.05) \times 10^{-5}$ $(4.31 \pm 0.09) \times 10^{-5}$ $(7.6 \pm 0.2) \times 10^{-5}$ $(1.26 \pm 0.05) \times 10^{-4}$	$\Delta G^{\ddagger}_{298}$ = 25.3 ± 0.4 kcal mol^{-1} $\Delta H^{\ddagger}$ = 12.7 ± 0.3 kcal mol^{-1} $\Delta S^{\ddagger}$ = −42.4 ± 0.4 cal mol^{-1} K^{-1} E_a = 13.4 ± 0.3 kcal $mole^{-1}$ ln A = 9.3 ± 0.4
4	$n\text{-}Bu_4NI$	338 343 348 358 368	$(5.0 \pm 0.2) \times 10^{-4}$ $(9.17 \pm 0.09) \times 10^{-4}$ $(1.45 \pm 0.06) \times 10^{-3}$ $(3.3 \pm 0.1) \times 10^{-3}$ $(9.8 \pm 0.2) \times 10^{-3}$	$\Delta G^{\ddagger}_{298}$ = 24 ± 4 kcal mol^{-1} $\Delta H^{\ddagger}$ = 23 ± 2 kcal mol^{-1} $\Delta S^{\ddagger}$ = −5 ± 5 cal mol^{-1} K^{-1} E_a = 24 ± 2 kcal $mole^{-1}$ ln A = 28 ± 3

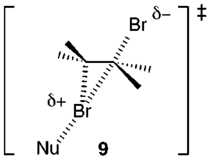
posed in Scheme 1[2,3d] is consistent with the data. Both the anti-periplanar orientation of the two C−Br bonds (as in **7**) in the transition state and the second-order nature of the reaction contribute to the large negative values of $\Delta S^{\ddagger}$. One would expect the more nucleophilic iodide to give faster rates of debromination than dihexyltelluride **1**, which is reflected in the second-order rate constants.



7



8



9

The debromination of **4** with iodide has values of $\Delta H^{\ddagger}$ (23 kcal mol^{-1}) and E_a (24 kcal mol^{-1}) comparable to those observed for the debromination of **3** with both telluride **1** and iodide, but has a small negative value of $\Delta S^{\ddagger}$(−5 cal mol^{-1} k^{-1}). The more highly branched nature of **4** would permit more facile cleavage of a C−Br bond to carbocation and bromide. The polarization of the C−Br bond by the approach of iodide might be a sufficient driving force to induce loss of bromide with or without the anti-periplanar orientation of both C−Br bonds (as in **8**). A smaller negative value of $\Delta S^{\ddagger}$ would be expected with less ordering in the transition state.

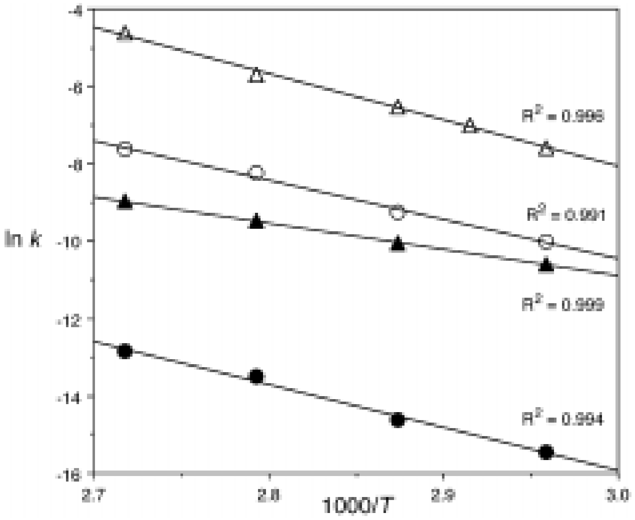


Figure 1. Eyring activation parameters from a plot of $R[\ln(k/T) - \ln(Nh/R)]$ vs 1000/T where k is the second-order rate constant at temperature T, R is the gas constant, N is Avogadro's number, and h is Planck's constant. The slope is equal to $-\Delta H^{\ddagger}$ in kcal mol^{-1}, and the intercept is equal to $\Delta S^{\ddagger}$ in cal mol^{-1} K^{-1}. Values are compiled in Table 3. Error limits for the second-order rate constants k are contained in Table 3 (all values are ≤0.07 on the natural log scale of the figure). Filled circles: debromination of 1,2-dibromodecane (**3**) with dihexyltelluride (**1**). Open circles: debromination of **3** with Bu_4NI. Filled triangles: debromination of 2,3-dibromo-2-methylpentane (**4**) with **1**. Open triangles: debromination of **4** with Bu_4NI.

Debromination of **4** with telluride **1** follows a different mechanistic path. The reaction is an entropy-driven

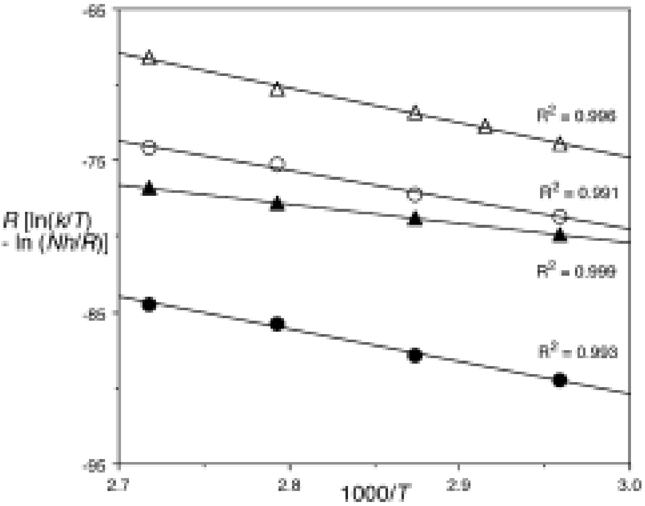
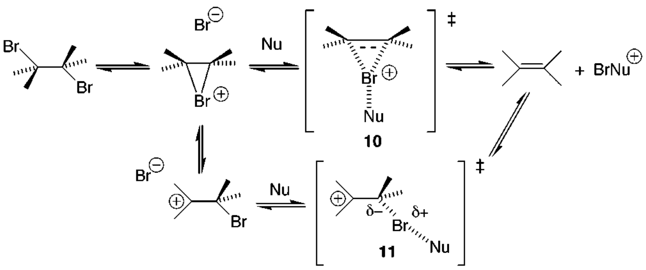


Figure 2. Arrhenius activation parameters from a plot of ln *k* vs 1000/*T*, where *k* is the second-order rate constant at temperature *T*. The slope is equal to $-E_a/R$, and the intercept is equal to ln *A*. Values are compiled in Table 3. Error limits for the second-order rate constants *k* are contained in Table 3 (all values are ≤0.07 on the natural log scale of the figure). Filled circles: debromination of 1,2-dibromodecane (**3**) with dihexyltelluride (**1**). Open circles: debromination of **3** with Bu_4NI. Filled triangles: debromination of 2,3-dibromo-2-methylpentane (**4**) with **1**. Open triangles: debromination of **4** with Bu_4NI.

Scheme 3



process ($\Delta S^‡ = -42.4$ cal mol^{-1} K^{-1}) with low barriers for both $\Delta H^‡$ and E_a (12.7 and 13.4 kcal mol^{-1}, respectively). These data suggest a highly ordered transition state in which partial bond breaking has occurred prior to approach of the debrominating agent. Earlier studies of *vic*-dihalides derived from steroids argue that halonium ion intermediates are readily formed under mild conditions.[7] Either nucleophilic attack of **1** on a dibromide with partial C−Br cleavage and partial bromonium ion character (as in **9**) or nucleophilic attack of **1** on a bromonium ion intermediate (as in **10** in Scheme 3) offers a scenario for a large negative value of $\Delta S^‡$ and small values of $\Delta H^‡$ and E_a. In both scenarios, significant bond breaking has occurred prior to nucleophilic attack of debrominating agent, which would contribute to the small values of $\Delta H^‡$ and E_a observed. The added ordering in transition state **9** relative to **7** is apparent with respect to rotational freedom. Transition state **10** imposes the order derived from partial bonding of the bromonium ion as opposed to a transition state from a less ordered carbocation as in **11**.

The bromonium ion path of Scheme 3 is also consistent with the second-order kinetics observed for the debromination of **4** with **1**. The concentration of bromonium ion from a first-order process in *vic*-dibromide **4** would change proportionally with the concentration of **4**. Thus, the second-order kinetics would still be first order in both telluride **1** and *vic*-dibromide **4**.

Summary

In summary, the bromination of olefins and subsequent debrominations of the resulting *vic*-dihalides offer a means for protection of the carbon−carbon double bond in synthesis. With strongly nucleophilc debrominating agents such as iodide and and, perhaps, aryltelluride anions, debrominations of *vic*-dibromides are initiated by nucleophilic attack at one bromine. With less nucleophilic debrominating agents such as dihexyltelluride (**1**), the propensity of the *vic*-dibromide to form bromonium ion intermediates determines relative reactivity. The divergence in mechanistic paths should permit the selective protection/deprotection of olefins with different substitution patterns.

Experimental Section

General Methods. Telluride **1** and *vic*-dibromides **3**−**6** were prepared according to ref 4a. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian 400 MHz instrument with residual solvent signal as internal standard (δ 7.26 for proton). Tetrabutylammonium iodide and $CDCl_3$ were used as received from Aldrich Chemical Co.

General Procedure for Kinetics Experiments. A. Reaction Order Experiments. Stock solutions containing 0.40 M 1,2-dibromodecane (**3**) and either 0.40 M telluride **1** or 0.40 M Bu_4NI were prepared in $CDCl_3$ as were stock solutions containing 0.40 M 2,3-dibromo-2-methylpentane (**4**) and either 0.40 M telluride **1** or 0.40 M Bu_4NI in $CDCl_3$. The stock solutions and 2-fold (0.2 M in each reagent) and 4-fold (0.1 M in each reagent) dilutions were sealed in NMR tubes and placed in a constant-temperature bath at 338 K. The solutions were sampled periodically by ^1H NMR spectroscopy and data was collected over the initial 10% of reaction for 1,2-dibromodecane (**3**) and over the initial 20% of reaction for 2,3-dibromo-2-methylpentane (**4**) using residual $CHCl_3$ as an internal standard. For these systems and the other systems described below, the olefinic protons, the protons on carbon-bearing bromine in the *vic*-dibromides, the α-methylene protons of both telluride **1** and Te(IV) dibromide **2**, and the α-methylene protons of Bu_4NI were well separated at 400 MHz. A plot of $[A]_t/[A]_0$, where [A] is the concentration of substrate, as a function of time gave the initial slopes, which were multiplied by $[B]_0$, where $[B]_0$ is the initial concentration of debrominating agent, to give the reaction velocities compiled in Table 1. Values are the average of duplicate runs.

B. For Pseudo-First-Order Reactions. Stock solutions of telluride **1** and Bu_4NI were prepared at 0.2, 0.4, 0.6, and 0.8 M. Ten-milliliter aliquots of the stock solution were transferred to a septum-sealed vessel containing 0.25 mmol of the *vic*-dibromide substrate (0.025 M in *vic*-dibromide). The solution was outgassed under a stream of argon bubbles. The reaction vessel was placed in a constant-temperature bath. At appropriate time intervals over 1−2 half-lives, 0.8-mL aliquots were withdrawn from the reaction mixture and the samples were analyzed by ^1H NMR spectroscopy. Duplicate runs were repeated at each concentration of debrominating agent and temperature. The calculated pseudo-first-order rate constants for debromination were plotted as a function of telluride or iodide concentration with the slope of the resulting line giving the second-order rate constants compiled in Tables 2 and 3. Values of *k* and 2σ are based on all runs as calculated by the program Sigma Plot (Version 4.16, Jandel Scientific).

---

[7] (a) Grob, C. A.; Winstein, S. *Helv. Chim. Acta* **1952**, *35*, 782. (b) Kwart, H.; Weisfield, L. B. *J. Am. Chem. Soc.* **1956**, *78*, 635. (c) Barton, D. H. R.; King, J. F. *J. Chem. Soc.* **1958**, 4398. (d) Alt, G. H.; Barton, D. H. R. *J. Chem. Soc.* **1954**, 4284. (e) Barton, D. H. R.; Rosenfelder, W. J. *J. Chem. Soc.* **1951**, 1048.

C. Arrhenius and Eyring Activation Parameters. Arrhenius activation parameters were obtained from a plot of ln k as a function of 1000/T (Figure 2) to give a line with slope of $-E_a/R$ and with an intercept of ln A, where k is the second-order rate constant for debromination and R is the gas constant. Eyring activation parameters were obtained from a plot of $R[\ln(k/T) - \ln(Nh/R)]$ as a function of 1000/T (Figure 1) to give a line with slope of $-\Delta H^{\ddagger}$ and an intercept of $\Delta S^{\ddagger}$, where R is the gas constant, k is the second-order rate constant, N is Avogadro's number, and h is Planck's constant. For the systems of this study, values of Eyring and Arrhenius activation parameters are listed in Table 3.

Acknowledgment. The authors acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

JO990332Q