Absolute Kinetic Rate Constants and Activation Energies for the Formation of Grignard Reagents

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This paper reports the first absolute rate constants for the formation of Grignard reagents from magnesium metal and organohalides. The theory that allows calculation of heterogeneous rate constants from the rate of growth of individual pits is described. By monitoring the reaction of individual reactive sites on the magnesium surface using photomicrography, it is possible to determine the rate of reaction and the active surface area; rate constants then are calculated from those data. Rate constants are on the order of 10^{-4} cm/s and vary relatively little between various organohalides. By measuring rate constants over a range of temperatures, Arrhenius parameters are determined for the reaction. The magnitudes of the enthalpic and entropic barriers are not consistent with electron transfer as the rate-limiting step. Rather, the data suggest that the rate-limiting step is reaction of the organohalide at the magnesium surface with partial insertion of a magnesium atom into the carbon-halide bond in the transition state.

Introduction

Organohalides react with magnesium metal to form organomagnesium halides. These reagents were described by Victor Grignard, who did much of the earliest work with the reaction.[1] However, almost a century after their first description, the mechanism of formation of Grignard reagents from organohalides and magnesium metal is still vigorously debated.[1−25]

It has been suggested that the first step of the reaction is a single electron transfer from the magnesium to the alkyl halide to form a radical anion, which may or may not have a significant lifetime.[26,27] This radical anion would cleave very rapidly to form a halide anion and an organic radical. Evidence has been presented that suggests that the first step appears to be the rate-limiting step.[9,10]

Many aspects of the reaction of organohalides with magnesium are not clearly understood, and most of the complications lie at the metal surface. The major hindrance to answering these questions is the lack of absolute rate constants for the formation of Grignard reagents. Many authors have noted that because the active area of the magnesium surface is unknown and continuously changing, absolute rate constants have not been determined.[9−12,19,23−25] In the absence of absolute rate constants, relative rates have been measured for a wide variety of organohalides and solvents, and many questions have been answered. For example, a number of possible transition states have been rejected.[9−12]

In the past 10 years, studies of the kinetics of heterogeneous chemical reactions have emphasized the importance of microscopic imaging of surfaces during the reaction.[e.g., 28−37] For an excellent review, see ref 37.

We have described a flow cell for microscopic observation of magnesium surfaces during Grignard reagent formation.[23,24] We observed that discrete reactive sites formed, and the pits assumed the shape of a hemisphere.[23] By measuring the pit radius as a function of time, the rate at which the reaction is proceeding in the pit may be determined. In this paper, we develop the mathematics for using these measurements to determine the absolute heterogeneous rate constants of Grignard reagent formation. We then use this method to determine rate constants as well as enthalpies and entropies of activation for the formation of a variety of Grignard reagents.

Our results are not consistent with simple electron transfer being the rate-limiting step. Rather, the transition state is more likely an organohalide associated with the magnesium surface, and the carbon-halide bond is partially broken.

Experimental Section

Reagents. HPLC grade tetrahydrofuran was purchased from Fisher Scientific and distilled from sodium/benzophenone under argon. Alkyl halides were purchased from Aldrich and dried by passage down a short column of dry alumina. Magnesium strips were cut (99.9% Fisher, 0.17 mm thick × 3.2 mm wide), manually polished just before use with Buehler LTD Carbimet 600 grit grinding paper, and wiped with a Kimwipe. Solutions of organohalide and THF were injected into the flow cell with a 30-mL syringe.

Flow Cell. The flow cell that allowed in situ photomicrography of the magnesium surface has been described in detail previously.[23,24] To maintain temperature control, a modified flow cell was fitted with a stainless steel jacket through which water was pumped using a MT Lauda thermostated circulating bath. The temperature inside the flow cell adjacent to the magnesium strip was monitored with a YSI Model 43 Tele-thermometer and a Teflon-coated thermoprobe inserted through a side port of the cell. The thermoprobe in the cell also allowed us to confirm that the heat from the exothermic reaction is rapidly dissipated and does not affect significantly the temperature at which the reaction proceeds. No indicator was used, in contrast to earlier studies.[23,24]

Instruments. Photomicrographs were recorded and analyzed using a Nikon SMZU binocular microscope, a JVC video

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camera, and a Leica Quantimet 500MC Image Analysis System. Typically 10 to fourteen pits were measured at six or more times as they grew from 15 to 100 microns in radius. Plots of radius vs time were prepared for each pit, and the slope was determined by linear regression. Reproducibility within a single experiment was estimated by calculating the relative standard deviation (rsd) of the slopes. Reproducibility between experiments was estimated by determining the rsd of the average slopes determined on different days.

As a general rule, solution was only flowed through the cell when necessary to refresh the solution and maintain a relatively constant organohalide concentration (i.e. no more than 10% depletion). To test for the effect of convection, in two experiments solution was continuously flowed through the cell using a syringe pump (Orion Sage Model 365).

Determination of Pit Morphology. To determine pit morphology, we removed magnesium strips from the reactive mixture after pit formation, rinsed with THF, and dried. We measured the radius of the pit in the horizontal plane of the magnesium surface using a binocular microscope and micrometer eyepiece. We measured the depth of the pit using a Narishige 12003 Micromanipulator fitted with a glass tip (<20 micron radius). This method underestimated the pit depth by about 5−10 microns. The precision of the measurements was ±5 microns.

Product Analysis. To ascertain that we were indeed measuring the kinetics of Grignard reagent formation, we flowed the products of the reaction from the flow cell into a flask containing acetone (99.9+% HPLC grade purchased from Sigma-Aldrich) and hydrolyzed. Product analysis using a Hewlett-Packard G1800B gas chromatograph-mass spectrometer (gc-ms) indicated >95% yield of Grignard reagent inside the flow cell.

Theory

In earlier papers, we reported that the radius of pits in the magnesium surface increases linearly with time.[24] In this section, we show that this observation is consistent with a reaction that is proportional to the reactive surface area of magnesium. Further, it indicates that there is a significant energy barrier to formation of Grignard reagents. This appears to contradict earlier evidence that the formation of Grignard reagents is frequently mass-transport controlled,[10] but there is no contradiction. Diffusion to very small sites is much faster[38−43] than mass transport by convection, allowing us to observe the rate of reaction.

It is possible to describe the rate of reaction as a function of the change in volume of the pit by eq 1

$$dV/dt = \text{rate}(V_m) \qquad (1)$$

where V is the volume of the pit (cm^3), t is the time of reaction (sec) rate is the rate of formation of Grignard reagent at that specific reactive site (mol/sec), and V_m is the volume of one mole of magnesium (14.0 cm^3/mol).

Because the pits are hemispherical,(vide infra for experimental determination of pit morphology) the volume of the pit is described by eq 2 where r is the pit's radius (cm)

$$V = (2/3)\pi r^3 \qquad (2)$$

Taking the derivative of both sides of eq 2 yields eq 3

$$dV/dt = 2\pi r^2(dr/dt) \qquad (3)$$

If the rate is determined by a surface reaction requiring significant activation energy, the rate law is

$$\text{rate} = k_s C^n A \qquad (4)$$

where k_s is the heterogeneous rate constant (cm/s if n=1), C is the bulk organohalide concentration (mol/cm^3), n is the order of reaction, and A is the surface area of the pit (cm^2). By combining eqs 1, 3, and 4 with the surface area of a hemispherical pit ($A = 2\pi r^2$), the slope of r as a function of time is predicted to be

$$dr/dt = k_s C^n V_m \qquad (5)$$

On the other hand, if the rate is mass transport controlled, and mass transport relies on diffusion[38−43] to a disc-shaped site, the rate is described quantitatively as

$$\text{rate} = 4DCr \qquad (6)$$

where D is the diffusion coefficient (cm^2/sec). Although diffusion to a hemispherical pit has not been quantitatively defined, the equation is certainly similar to eq 6. For example, diffusion to a hemispherical site protruding from the surface is described quantitatively by eq 7[42]

$$\text{rate} = 2\pi DCr \qquad (7)$$

If eq 6 is substituted into eq 1, then eq 8 results

$$dV/dt = 55.9DCr \qquad (8)$$

Substituting eq 3 into eq 8 and rearranging yields eq 9

$$dr/dt = 8.9DC/r \qquad (9)$$

Integration of eq 9 yields eq 10

$$r^2 = 2(8.9)DCt \qquad (10)$$

Equation 11 results from taking the square root of both sides of eq 10

$$r = 4.2(DC)^{1/2}t^{1/2} \qquad (11)$$

Equation 11 predicts that the radius of the pit is not a linear function of time, but rather r would depend on the square root of t if diffusion controls the rate of reaction.

On the other hand, integration of eq 5 yields eq 12, which predicts r to be a linear function of time when there is a significant energy barrier to the reaction

$$r = k_s C^n V_m t \qquad (12)$$

Results

We have measured the growth of thousands of pits as a function of time and found that plots of radius vs time are linear. Almost invariably, plots are fit nicely by linear regression, consistent with eq 12 and kinetic control of reaction rate. (For illustrations, see Figure 3 in ref 23 and Figure 2 in ref 24.)

Does Mass Transport (Diffusion) Control the Reaction Rate? In addition to the linearity of plots of r vs t, three additional sets of experiments are consistent with kinetic control of the formation of Grignard reagents: pit morphology, absolute rate of growth, and the effect of convection.

Morphology of Pits. It has been demonstrated both theoretically and experimentally that diffusion to small sites results in much higher flux to the edge of the site than to the center.[39−42]

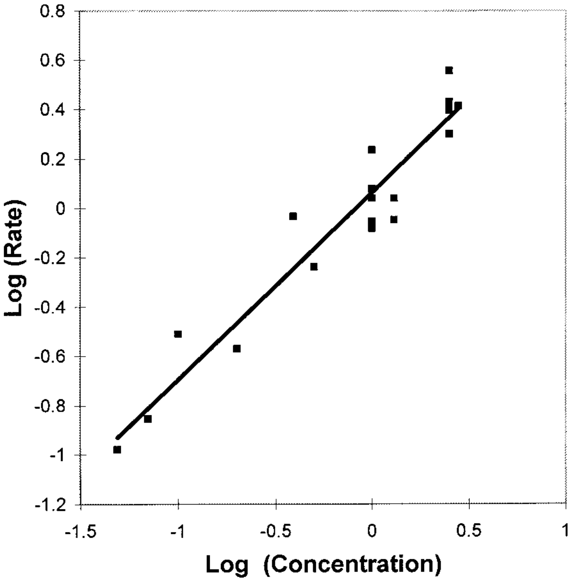


Figure 1. Log−log plot of the rate of growth of pits [log(d*r*/d*t*)] vs molarity [log(mol/L)] of bromoethane in THF at 23 °C.

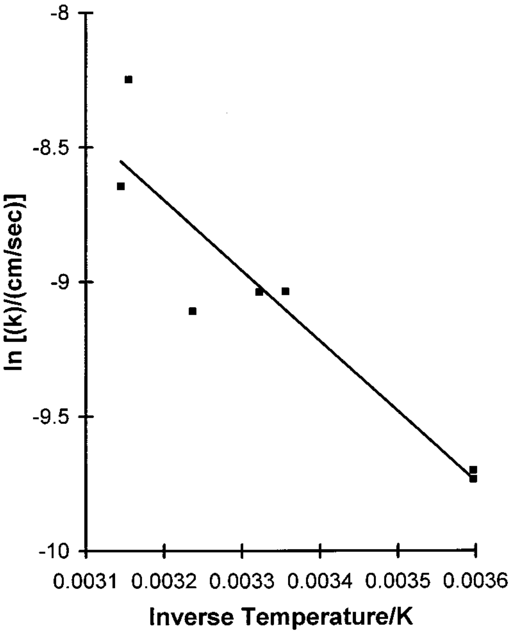


Figure 2. Arrhenius plot for Grignard reagent formation from bromobenzene between 5 °C and 55 °C.

If the rate is diffusion controlled and diffusion is greatest to the edge of the site, the edges of the pit will be etched away more rapidly than the bottom of the pit. Thus, under diffusion control, pits should be much wider than they are deep. In contrast, under kinetic control, all portions of the pit will react (and thus grow) equally rapidly resulting in a hemispherical pit.

To determine pit morphology, we have measured the width and depth of 18 pits in five separate experiments. The data are provided in Table 1. The average ratio of width:depth is 1.06. Within the accuracy of our determination, this ratio corresponds to hemispherical pits. The morphology of the pits in the magnesium allows rejection of the hypothesis that mass transport (in our case, diffusion) controls the rate of the formation of Grignard reagent.

TABLE 1: Ratios of Pit Radius to Pit Depth for 18 Pits in Five Separate Experiments

pit	depth/μm	radius/μm	ratio
1	93	100	1.08
2	69	72	1.05
3	80	70	0.88
4	45	54	1.19
5	50	57	1.14
6	53	50	0.95
7	45	50	1.11
8	60	70	1.16
9	95	100	1.05
10	80	78	0.98
11	70	86	1.21
12	59	60	1.03
13	83	88	1.06
14	153	150	0.98
15	105	107	1.02
16	45	50	1.11
17	60	64	1.07
18	50	50	1.00
			Mean = 1.06

Rate of Pit Growth Predicted by Mass Transport Control. Because all terms of eq 9 can be independently determined, it is possible to calculate the expected rate of pit growth that would result if diffusion controlled the reaction rate. At 1.0 M organohalide in THF with $D = 3.0 \times 10^{-5}$ cm^2/sec, a diffusion controlled reaction in a 25 micron pit would result in pit growth of d*r*/d*t* = 1.0×10^{-4} cm/sec, about 50 times faster than what we observe for bromoethane. For 2-chloropropane, eq 9 predicts a rate about 200 times greater than that observed. Thus, pit growth is much slower than that expected from diffusion control.

Effect of Convection on Rate. To further confirm that mass transport does not limit the rate of reaction of bromoethane with magnesium under our experimental conditions, we continuously flowed the solution through our reaction cell. (Normally, the solution only flows at brief intervals as necessary to maintain a constant organohalide concentration.) In two different experiments, with flow rates of 0.5 and 1.0 mL/min rates (corresponding to linear velocities of 5 and 10 cm/min inside the cell), convection did not increase the rate of reaction. This is inconsistent with a reaction rate limited by mass transport.

Finally, we note that other studies using strategies very different from ours also have suggested that Grignard reagent formation is not mass transport controlled under conditions of rapid mass transport.[16,25,44]

Determination of the Order of Reaction, *n*. Equation 12 shows that the rate of the growth of pits, d*r*/d*t*, should depend on C^n where *n* is the order of the reaction. To determine the order, we have measured d*r*/d*t* in 23 experiments over a 70-fold range of the concentration of bromoethane (0.04 to 2.8 M). A plot of d*r*/d*t* vs concentration appears linear. When log(d*r*/d*t*) is plotted vs log(concentration), the slope is 0.72 suggesting a slight curvature of the plot of rate vs concentration. (See Figure 1.) The slight curvature is most simply interpreted as indicating that the order is one, and the medium slightly affects the rate.

Alternatively, an apparent fractional order would result if there were a slow growth of the pits independent of organohalide concentration superimposed on the first order reaction (becoming proportionately more important at lower concentrations of organohalide). To exclude the possibility of a second reaction affecting our plots, after initiating pits with bromoethane we flushed a reaction cell with pure THF. No pit growth was detected in the absence of organohalide. We repeated the experiment with THF containing 1% water and saturated with oxygen at 1 atm and again observed no pit growth.

TABLE 2: Heterogeneous Rate Constants, Number of Determinations (N), and Relative Standard Deviations (rsd) for the Formation of RMgX from Organohalide at 23 +1ºC.

organohalide	$k \times 10^5$/(cm/s)	N	rsd
2-chloro-2-methylbutane	4.9	3	13%
2-chloropropane	6.0	2	
2-bromobutane	7.2	1	
1-chlorobutane	7.4	2	
bromocyclopentane	7.4	3	12%
bromobenzene	8.4	7	21%
bromocyclopropane	11	1	
bromoethane	12.6	23	26%
benzyl bromide	13.6	1	

We have measured reaction rates as a function of the concentration of bromobenzene also, and the results are similar to those for bromoethane.

Determination of Rate Constants for Grignard Reagent Formation. Using eq 5 and the slopes of radius vs time, we have calculated heterogeneous rate constants at 23 ±2 °C for the reaction of magnesium with a wide range of organohalides in THF. The results are summarized in Table 2. As an indication of the precision of these values, the relative standard deviation (rsd) of slopes determined in a single experiment is typically about 35% (indicating the reproducibility between pits in the same surface). For the 23 different experiments with bromoethane, the rsd for the determined rate constant is 25% (indicating the day-to-day reproducibility). Although there were fewer replicates, the day-to-day reproducibility of k_s for other organohalides ranges from 10 to 26% (see Table 2).

The rate constants reported in Table 2 vary relatively little between organohalides. For example the reaction of bromoethane with magnesium is about twice as fast as the reaction of 2-chloro-2-methylbutane. However, comparing the rate constants for bromoethane, bromobenzene, and 2-chloro-2-methylbutane using a Student's t-test[45] shows that these values are all significantly different from each other.

The small (but significant) variation in k_s is surprising in view of the wide range of relative values reported by Whitesides et al.[9,10] On the other hand, we have shown that the overall rate of Grignard reagent formation depends on at least three factors: the time for initiation, the number and size of active sites, and the rate of reaction.[24] It is possible that, for example, the number of active sites have affected the determination of *relative* rates. In support of our results, in a recent study that suggested kinetic control of Grignard reagent formation, those authors also reported small differences in the rates of reaction of bromoalkanes and chloroalkanes.[25]

The significant difference in bond energies between C−Br and C−Cl also make the small variation in k_s surprising. The bond energy should have a direct effect on the enthalpy of activation if there is breakage of the bond in the transition state. To further investigate the contribution of the carbon-halide bond strength, we have measured rate constants over a range of temperatures in order to determine Arrhenius parameters.

Arrhenius Parameters for Grignard Reagent Formation. The dependence of the heterogeneous rate constant on temperature is described by eq 13, one form of the Arrhenius equation[46−48]

$$k_s = \kappa\, Z_s \exp[\Delta S^{\ddagger}/R] \exp[-\Delta H^{\ddagger}/RT] \tag{13}$$

In eq 13, κ is the transmission coefficient (normally one). Z_s is the heterogeneous collision frequency, which may be calculated from eq 14, where m is the mass of the reacting molecule and k is Boltzmann's constant.[46−48] (For example, Z_s = 4970 cm/s for bromobenzene.)

TABLE 3: Arrhenius Parameters for Grignard Reagent Formation of Three Organohalides, for Reversible Electron Transfer (ET),[46−52] and for Reductive/Cleavage of Alkyl Halides (RX/R·+X⁻)[26,27]

organohalide	$\Delta H^{\ddagger}$ (kJ/mol)	$\Delta S^{\ddagger}$ (J/mol-K)	$\Delta G^{\ddagger\,a}$ (kJ/mol)
2-chloro-2-methylbutane	32	−50	46
bromobenzene	22	−80	45
bromoethane	25	−60	44
electron transfer	10 to 25	+10 to −25	8 to 25
$RX/R\cdot + X^-$			60 to 90

[a] At T = 295 K.

$$Z_s = (kT/2\pi m)^{1/2} \tag{14}$$

When $\ln(k_s)$ is plotted vs $1/T$, the slope is $-\Delta H^{\ddagger}/R$ and the intercept is $\{\kappa\; Z_s\; \exp[\Delta S^{\ddagger}/R]\}$. We have measured k_s for bromobenzene at five different temperatures between 5 and 55 °C. The Arrhenius plot over this range is linear (Figure 2), and the slope allows an estimate of the enthalpy of activation to be 22 kJ/mol with a standard error of ±3.7 kJ/mol. The Arrhenius plot for bromoethane yields an enthalpy of activation comparable to that for bromobenzene (25 kJ/mol).

The Arrhenius plot for 2-chloro-2-methylbutane yields an enthalpy of activation of 32 kJ/mol (±5.7 kJ/mol). (See Table 3.) The difference between the values of $\Delta H^{\ddagger}$ for the chloro and bromo compounds is not only statistically significant, it is also of the magnitude expected based on the greater strength of the C−Cl bond if the bonds are partially broken in the transition state.

Extrapolation of the Arrhenius plot to the y-intercept makes the determination of the entropy of activation less precise than the enthalpy of activation. However, for 2-chloro-2-methylbutane, bromoethane, and bromobenzene, the entropy of activation poses a relatively large barrier of −50 to −80 J/K−mol.

More simply, it is possible to determine $\Delta G^{\ddagger}$ directly from the rate constant using eq 15.[46−48] These values are also reported in Table 3

$$k_s = \kappa\, Z_s \exp[-\Delta G^{\ddagger}/RT] \tag{15}$$

Does Residual Water Complicate the Kinetic Studies? Because of the relatively high surface/volume ratio of the flow cell, we were concerned that water might affect our kinetic measurements. However, as noted above, intentionally added water and oxygen does not cause corrosion of magnesium on the time scale of our experiments in the absence of organohalide. Furthermore, we have noted that initiation times for the reaction vary greatly depending upon the care of solvent preparation (from one to 60 min), but the rate constants are unaffected by solvent preparation. Presumably, this is because once the reaction does initiate, the Grignard reagent that is produced scavenges any residual water that may have initially been present in solution.

To measure reaction progress under a more conventional experimental setup, we reacted magnesium with 10 mL of 1.0 M bromoethane in THF in a small flask covered with a microscope slide. The rate constant determined in this way was not different from those measured in the flow cell.

Discussion

In this paper, we present evidence that Grignard reagent formation must overcome a significant energy barrier and is not mass transport controlled under conditions of rapid diffusion. First-order heterogeneous rate constants are on the order of 10^{-4} cm/s. By measuring rate constants over a range of temperatures, we have determined that about half of the free energy barrier to this reaction at room temperature is due to the entropy of activation. (See Table 3.) The small dependence of the rate constant upon the nature of the halide (Br or Cl) is partially due to the large contribution of entropy to the total free energy barrier.

To draw conclusions from these data about the rate-limiting step in Grignard reagent formation, it is necessary to compare these values to those for reactions that are possibly related. Comparable data have been reported for: (1) uncomplicated heterogeneous electron transfer, (2) irreversible electron transfer to alkyl and aryl halides (studied by both spectroscopic and electrochemical techniques).

We have surveyed the literature for Arrhenius parameters for uncomplicated electron transfer (ET) to organic and organometallic molecules in a wide variety of nonaqueous solvent including THF. (See refs 46 and 48−52 and references therein.) These reactions show a range of enthalpies of activation from 10 to 25 kJ/mol. Thus, the enthalpy of activation we measure for bromoethane and bromobenzene reacting with magnesium are within this range (albeit at the high end), whereas our value for the reaction of 2-chloro-2-methylbutane is outside of this range.

On the other hand, the entropic barrier to uncomplicated ET (+10 to −25 J/mol−K) is much smaller than we measure for any of our compounds, resulting in a smaller free energy barrier and much larger rate constants for ET relative to Grignard reagent formation. This comparison suggests that the rate-limiting step for Grignard reagent formation is not simple ET.

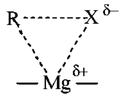
Further supporting the rejection of ET as the rate-limiting step is the lack of correlation between half-wave voltages for the reduction of RX and their rates of Grignard reagent formation (using either our absolute rate constants or others' relative rates[9−12,25]).

A second source of data that may be compared to ours is the spectroscopic studies of the kinetics of irreversible homogeneous electron transfer from polyaromatic anions to alkyl halides.[53,54] These studies have shown a dramatic dependence of rate on the halide (I, Br, Cl, or F) as well as rates that correlate well with half-wave voltages for the reduction of the organohalides. Thus, the rate-limiting steps must be very different between homogeneous ET to alkyl halides and Grignard reagent formation.

Of most direct significance to Grignard reagent formation are the studies of Saveant et al.[26,27,55] Using direct electrochemical techniques as well as redox catalysis, the kinetics and thermodynamics of heterogeneous and homogeneous ET to organohalides are well understood.

Perhaps most revealing, the free energy of activation for electron transfer to organohalides (at their E°) is 60−90 kJ/mol, significantly greater than the free energy of activation of Grignard reagent formation (see Table 3). This could be explained if the E° for the $Mg^{0/2+}$ couple were negative of the E° of the organohalide, but this is not the case. The E° for $Mg^{0/2+}$ is −2.3 V vs Ag/AgClO$_4$ (−2 V vs SCE)[56] approximately 0.5 V positive of both the E° of bromobenzene[26] and of the peak potentials for the heterogeneous reductions of alkyl bromides.[27]

All of these comparisons allow a rejection of the hypothesis of electron transfer as the rate-limiting step in Grignard reagent formation. Rather, we propose that the rate-limiting step is reaction of the organohalide with a magnesium atom at the surface. The transition state in the rate-limiting step probably resembles structure *1*, which is consistent with all of our results. This species would have the very low entropy suggested by the high entropic barrier to the reaction. Furthermore, there is partial breakage of the bond consistent with the dependence of the enthalpy of activation on the halide.



(1)

Structure 1 is also consistent with all of the data presented by Whitesides et al.[9−12] They considered a wide range of possible transition states[9,11] and were unable to reject three of them: an anion, a radical, and a structure similar to 1. As discussed, our data are not consistent with either an anion or a radical. Structure 1 is also similar to the structure of the *intermediate* proposed by Walborsky et al.[3−6] Finally, our proposal that magnesium is directly involved in the cleavage of the organohalide bond is consistent with the free energy of activation being lower for Grignard reagent formation than for unassisted electron transfer/bond cleavage to organohalides.

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