here for synthesizing R_P-ATPγS,$\gamma^{18}O_2$ has been adopted by Webb and Trentham in their studies of the stereochemical courses of ATPases;[18] and these workers have also adapted the method to the synthesis of chiral ATPγS,γ^{17}O,^{18}O. The yields are good when appropriate precautions are taken to exclude water from the phosphoanhydride coupling reaction mixtures, and the method described for the synthesis of R_P- and S_P-ADPβS,β^{18}O has been adapted to the efficient synthesis of ADPβS from AMPS and **1**.[19]

A recent advance in the chemistry of phosphorothioates should make the chiral nucleoside [^{18}O]phosphorothioates described here increasingly important as synthetic precursors in the synthesis of ATP specifically enriched with isotopic oxygen at any position of the triphosphate moiety. It has been found that ATPβS,β-cyanoethyl-ADPαS and cyclohexyl propyl pyrophosphorothioate are desulfurized by reaction with cyanogen bromide in water at neutral to alkaline pH.[19,20] The reaction leads to the substitution of ^{18}O for sulfur in $H_2{}^{18}O$ and, in the case of β-cyanoethyl-ADP, with inversion of configuration.[20] By combining highly stereoselective and stereospecific phosphorylation[6,8] of R_P- and S_P-AMPS,^{18}O and R_P- and S_P-ADPβS,β^{18}O with desulfurization by cyanogen bromide, it should be possible for the first time to introduce isotopic oxygen specifically either into the P_α–P_β or the O_β–P_γ bridging positions of ATP or into either diastereotopic position at P_α or P_β of ATP. Similarly, R_P- and S_P-ADPα^{18}O as well as ^{18}O-bridging ADP(α–β)^{18}O an be synthesized. These specifically enriched species of ATP and ADP, heretofore inaccessible, will greatly facilitate isotopic studies probing the mechanisms of enzyme action.

The phosphorus configurations assigned in this paper are based upon the ^{31}P NMR chemical shifts of P_α in samples of R_P- and S_P-ADPαS produced in the chemical degradations of **4a**, **4b**, **5a**, and **5b**. Since the shifts for the epimers of ADPαS are known from earlier work, the configurational assignments are secure. Table I exemplifies the importance of exercising caution in the assignment of configurations by the use of ^{31}P NMR data. Note that the P_α chemical shift for R_P-ADPαS is downfield from that for the S_P epimer; this relationship extends to the epimers of ATPαS[8] and to the uridine series as well.[3c,j] The relationship does *not* extend to compounds **4a** and **4b** or **5a** and **5b**, since in these compounds the P_α chemical shifts for the S_P epimers are downfield from those for the R_P epimers. Therefore, any configurational assignments for **4a** and **4b** or **5a** and **5b** based on their relative P_α chemical shifts and the corresponding relative shifts for other nucleotides would have been erroneous. The measurement of ^{31}P NMR chemical shifts is a powerful technique for distinguishing the epimers of thionucleotides, but assignments of absolute configuration can be made only by chemical correlation with compounds of known configuration.

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Registry No. 1, 68973-49-9; **1** trioctylammonium salt, 81671-39-8; **2**, 68973-47-7; **3**, 68973-51-3; **4a**, 69010-05-7; **4b**, 68973-40-0; **5a**, 81671-40-1; **5b**, 81738-72-9; AMPS,$^{18}O_2$, 68973-48-8; AMPS,$^{18}O_2$ trioctylammonium salt, 81687-72-1; Rp-ATPγS,$\gamma^{18}O_2$, 68973-46-6; Sp-ADPαS,$\alpha^{18}O_2$ trioctylammonium salt, 81687-74-3; Rp-ADPβS,β^{18}O, 69182-10-1; Sp-ADPβS,β^{18}O, 68973-41-1; Rp-AMPS,^{18}O, 71067-08-8; Sp-AMPS,^{18}O, 71067-07-7; AMP trioctylammonium salt, 69098-20-0; Sp-ADPαS,$\alpha^{18}O_2$, 81687-75-4; Rp-ADPαS,$\alpha^{18}O_2$, 81687-76-5; adenosine, 58-61-7; 2′,3′-(methoxymethylidene)adenosine, 16658-10-9; 2,3-(methoxymethylidene)adenosine-5′-cyanoethylphosphate, 81671-41-2.

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The Barbier Synthesis: A One-Step Grignard Reaction?

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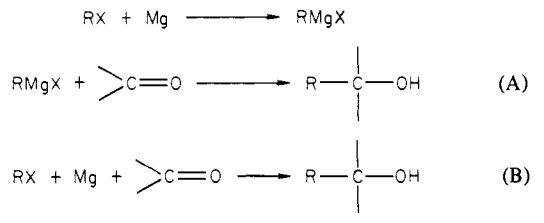
Contribution from the Institut de Topologie et de Dynamique des Systèmes, Université Paris VII, associé au C.N.R.S., 75005 Paris, France. *Received June 3, 1981. Revised Manuscript Received January 7, 1982*

Abstract: Counter to generally accepted theory, it is demonstrated that the Barbier synthesis does not necessarily involve the in situ formation of an organometallic compound. In certain cases, there is a radical pathway in which the anion radical ($R^{\cdot}X^{-}$) resulting from the attack by a halogenated derivative on lithium is directly trapped by the ketone or by the ketyl radical on the metal surface before the organometallic compound forms. This pathway can be unique, as when 1-bromoadamantane condenses with adamantanone or hexamethylacetone. However, by extension of the Barbier synthesis to other "cage-structure" compounds homologous to adamantane, it is seen that the radical pathway can compete with the organometallic pathway and that this competition is principally determined by the stability of the cage radicals generated at the metal–solution interface. An optimum yield can be attained in this type of synthesis by choosing the Grignard reaction or the Barbier reaction, depending on the nature of the halogenated cage derivatives in use.

The Grignard reaction,[1] which involves a first step for the synthesis of an organometallic compound and a second step for the reaction of the latter with a substrate (A), chronologically follows the Barbier synthesis,[2] which yields the end product in a single step (B). So long as use of the Grignard reaction was restricted to magnesium, it was preferred over the Barbier reaction and was studied to a greater extent from the viewpoint of synthesis



and from that of the reaction mechanisms. However, with the recent use of other metals, particularly lithium,[3-7] there has been

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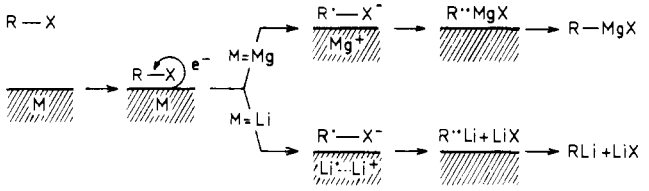
Scheme I



a renewal of interest in the Barbier reaction because it often results in exceptional yields.

Despite this renewal, there are very few mechanistic studies of the Barbier reaction, as it is generally assumed that it involves the transitory in situ generation of an organometallic compound, although this has never been explicitly demonstrated.[5,8,9] Nevertheless, doubt can be cast on this assumption. Indeed, the yields from both reactions, conducted under identical experimental conditions, are often highly divergent.[5] Moreover, CIDNP studies by Blomberg et al.[10] indicate that CIDNP signals observed during the formation of an organometallic compound are not detected for the Barbier reaction. Again, studies in this laboratory on the synthesis and reactivity of cage-structure organometallic compounds suggest that the cage radicals generated at the metal surface in the Barbier reaction mechanism behave differently from what has been reported elsewhere.[11-13] These observations have led to a reconsideration of this mechanism in an attempt to specify the role played by the intermediates generated at the metal surface when alkyl halide attacks lithium.

Results and Discussion

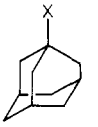
Studies on the generation of organomagnesium[14-19] and organolithium[20-24] compounds strongly point to a mechanism whereby an anion radical $R\text{-}X^-$, resulting from a single electron transfer between the metal and the halide, appears on the metal surface before formation of the organometallic compound. This anion radical would then evolve into an intimate pair of radicals (R··MgX or R··Li) to yield the organometallic compound (Scheme I). These steps would occur at *the metal surface.*

This contrasts with the condensation of an organometallic comound with a ketone, whether involving a radical or polar mechanism,[25] which occurs in the reaction medium.

The easiest way to determine whether formation of an organometallic compound is an intermediate step in the Barbier reaction would seem to be to attempt the Barbier synthesis under conditions that would prevent the organometallic compound from condensing with the ketone. To block condensation between a ketone (hexamethylacetone, **1**, or adamantanone, **2**) and 1-adamantyllithium (**3a**) we lowered the temperature so that no alcohol could form under these conditions.

Table I. Aging of Solutions of 1-AdLi in Ether at −20 °C

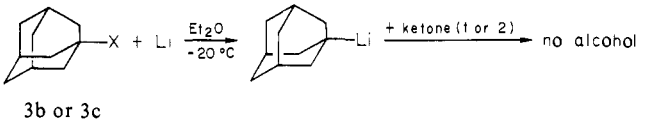
time, h	% AdLi (3a)	% AdH	% AdOH	% AdAd	% ethers
0	75	21	0.7	1.3	<1
1	70	25	2.5	1.3	<1
2.25	65	29	3.4	1.3	<1



3a, X = Li
3b, X = Br
3c, X = Cl

3a was synthesized in ethyl ether at −20 °C. Whether starting with **3b** or **3c**, deuterolysis samplings subjected to mass spectrometry analysis are composed of 75% organolithium compound, 20–22% adamantane, 1–2% biadamantane, and 2–3% 1-adamantanol. Samplings taken from the lithium solution at various points in time and subjected to deuterolysis indicate (Table I) that **3a** is surprisingly stable in this medium, as only a 5% loss in concentration occurs per hour.

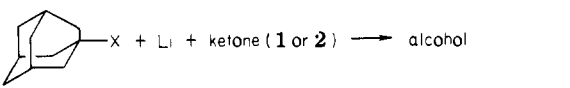
A stoichiometric amount of **1** or **2** is added to the lithium solution obtained in ether at −20 °C. Two hours later there is



3b or 3c

no trace of condensation alcohol in the deuterolysis sampling, and mass spectrometry analysis indicates a 70% presence of the deuterated adamantane. The ketones are enitrely recovered at the end of the reaction. Thus, in ether at −20 °C, **3a** does not react with **1** or **2** and does not yield any condensation alcohol. These experimental conditions are therefore ideal for the total hindrance of the organometallic pathway.

In contrast, the addition of stoichiometric amounts of ketone and of **3b** or **3c** to a slight excess of lithium powder in the presence of ether at −20 °C yields, after stirring for 45 m, 40% di-*tert*-butyladamantylcarbinol with **1** and 71% 2-(1′-adamantyl)-2-adamantanol with **2**.



3b or 3c

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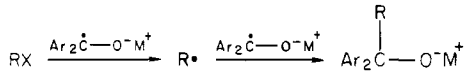
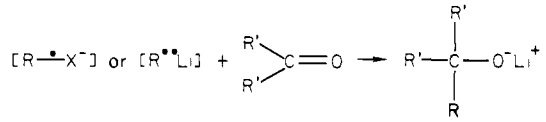
Thus, in tests with **1** and **2**, counter to generally accepted theory, no organometallic compound formation is observed for the Barbier reaction at −20 °C. The presence of biadamantane and of solvent attack products among the reaction byproducts hints at the existence of a radical pathway that impedes the formation of the organolithium compound.

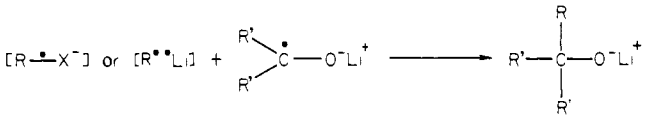
What are the species that react to yield the expected alcohol without the intermediacy of the organolithium compound formed in situ? Two hypothesis can be made: (a) reaction of the ketyl radical on the halide



and (b) reaction of transient species (R·X⁻ or R··Li) precursors of the organolithium compound on the ketone



or on the ketyl radical



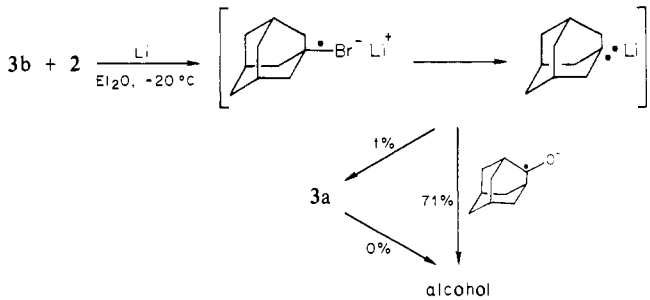
The first hypothesis was supported by studies[27] made on aromatic ketones, the ketyl radicals of which are particularly stable. Although it seemed very attractive and might account for some of our experimental results, one must remember that this mechanism advanced by Pearce et al.[4] was later refuted by these same authors[5] after the following experiments.

$$(C_6H_5)_2C{=}O + Li \xrightarrow{THF} (C_6H_5)_2\dot{C}{-}O^-Li^+$$

$$(C_6H_5)_2\dot{C}{-}O^-Li^+ + n\text{-BuBr} \not\rightarrow \text{alcohol}$$

We ourselves repeated this experiment with **2** and observed that, in the presence of **3b**, the ketyl radical only yields pinacol without the halide having undergone any reaction.[28] Thus, in the case of **2** also, hypothesis a can be rejected.

In the second hypothesis, the inervention of ketyl radicals from the ketone by reaction with the metal is proved by the presence of pinacol among the end products. Thus, the most probable hypothesis is a reaction between a transient species (R·X⁻ or R··Li), precursor of the organolithium compound, and a lithium adamantanone ketyl.



Nevertheless, the lifetime of these precursors must be very short, and one can wonder if this time is long enough to allow for a complete scavenging by the ketyl radicals. This is precedented in the work by Garst et al.[27] on the kinetics of the reaction between lithium benzophenone ketyl and several alkyl iodides. The second-order rate constant for combination of 5-hexenyl radicals with the ketyl was about 10^{-8} M^{-1} s^{-1}, i.e., near diffusion control, and the intermediate alkyl radical was completely scavenged by the ketyl.

Table II. Temperature Effects on the Barbier Reaction

temp, °C	% condensation alcohol	% RLi formed	% RH	% others
−20	71	1	17	11
−45	71	6	13	10
−65	71	10	14	5

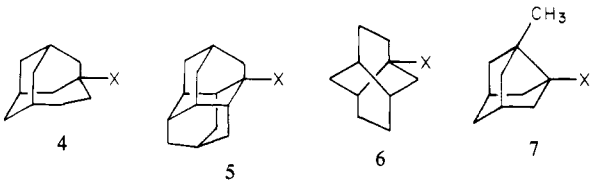
Since the organolithium compounds are known to be formed at the metal surface (Scheme I), the precursors (R·X⁻ or R··Li) are necessarily formed at the metal surface also. From thereon, if the alcohol forms before the organometallic compound, it is necessarily because the ketyl radical traps these species at the metal surface before they generate the organolithium compound. We are unable so far to choose between the radical anion or the radical pair for the transient precursor that is scavenged by the ketyl radical at the metal surface.

The overall results from both types of tests stress the importance of thermal effects in condensation reactions between a lithium compound and a ketone. Holm et al.[29] have reported an activation energy of ~8 kcal/mol for the reaction between dimethylallylmagnesium bromide and **1**. We have observed an activation energy of 10 kcal/mol for the condensation of 3,5,7-trimethyl-1-adamantyllithium with this same ketone.[30] Studies conducted by Cameron and Milton[9] prove that the Barbier reaction is practically unaffected by temperature, since the activation energy of bromobenzene on benzaldehyde in the presence of lithium is 0.8 kcal/mol, i.e., 10 times smaller than the above-mentioned values.

Several Barbier syntheses between **3a** and **2**[31] conducted under the same conditions but by varying the temperature from −20 to −60 °C (Table II) indicate that changes in temperature do not affect the yield of condensation alcohol. Thus, measuring thermal effects could be a suitable means of measuring subsequent competition between the radical and organometallic pathways in the Barbier synthesis involving halogenated derivatives other than **3b**.

Competition between Purely Radical and Organometallic Pathways

To examine the possibility of such a competition, we sought to determine the yields of condensation alcohol at two temperatures (−20 and −45 °C) for various cage-structure alkyl bromides such as 3-bromohomoadamantane (**4b**), 1-bromodiamantane (**5b**), 1-bromoadamantane (**3b**), 1-bromotwistane (**6b**), and 3-bromo-7-methylnoradamantane (**7b**).



a. X = Li; b, X = Br

For **4b** and **3b** the yields of condensation alcohol barely vary from one temperature to the other, whereas for **6b** and **7b** the difference in yields is more marked (Table III). Thus, for certain cage-structure compounds, only the radical pathway is detected, whereas for others it seems to be in competition with the organometallic pathway. In every case, the ketone yielding no condensation alcohol reacts with the metal and forms pinacol. If,

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(28) The instability of lithium adamantanone ketyl is so high that we were unable to keep it long enought to react it with a halide RX. This difficulty was overcome by reacting a stoichiometric mixture of **3b** and **2** with a solution of solvated electrons in HMPT. An instantaneous reaction yields 50% of adamantanone pinacol; 50% of **3b** is recovered unreacted.
(29) Holm, T. *Acta Chem. Scand. Ser. A* **1976**, *30*, 985.
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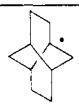
Table III. Product Yields from Barbier Reaction between Adamantane Homologues and Adamantanone

	RBr, %				
temp, °C	4b	5b	3b	6b	7b
−20, alcohol[a,b]	0	28	71	84	72
pinacol[a]	75[c]	40[d]	29	16	28
RLi[b]	0	0	1.0	3.5	5.5
hydrocarbons[b]	100	65	27.5	12.5	22.5
−45, alcohol[a,b]	0	36	71	66	20
pinacol[a]	75[c]	37[d]	29	34	80
RLi[b]	0	0	6	18	51
hydrocarbons[b]	100	65	23	16	29

[a] Yields calculated with respect to the ketone. [b] Yields calculated with respect to the halide. [c] 5% AdOH and 20% AdO remain in the medium. [d] There is 9% 2-AdOH and 10% AdO. The remainder results in a mass spectrum peak at *m/e* 151.

Table IV. Relative Stabilities of Cage Radicals

	R				
					
k[a]	46	6.5	1.0	3.5×10^{-2}	6.3×10^{-3}
colog k	−1.66	−0.81	0	+1.45	+2.20

[a] Correlated with or extrapolated from perester thermolysis scales.

as postulated, the radical pathway results from attack by the ketyl on precursors of the organometallic compound (anion radical or pair of radicals) before formation of the latter, the stability of these precursors should play a major role in the competition between the radical pathway and the organometallic pathway, if the latter exists. Actually, the stability of these species should be largely dependent on that of the cage radicals that constitute them. We have therefore sought to compare the yields obtained via the Barbier synthesis from various alkyl bromides with the stability of the corresponding cage radicals.

The most appropriate scale of radical stability is based on the thermolysis rate constants for peresters.[32] Missing data have been extrapolated from solvolysis rate constants[33] because, as certain authors have demonstrated,[34] there is a very good correlation between the carbocation and radical scales (Table IV).

Figure 1 depicts yields from the Barbier reaction vs. the cologarithm (colog k) of the thermolysis rate constant for peresters. The curves show that at −20 °C, at the same time as the yield of condensation alcohol increases from homoadamantyl to twistyl radicals and then decreases for methylnoradamantyl radical, there is an increase in the amount of free organolithium compound in the medium.

At −45 °C the results improve slightly for diamantyl radical[35] and remain unchanged for adamantyl radical. However, for the cage radicals less stable than adamantyl radical (i.e., twistyl and methynoradamantyl radicals), the temperature effect increases as the stability of the radical decreases; therefore, the yields in condensation alcohol decrease and the concentrations of residual

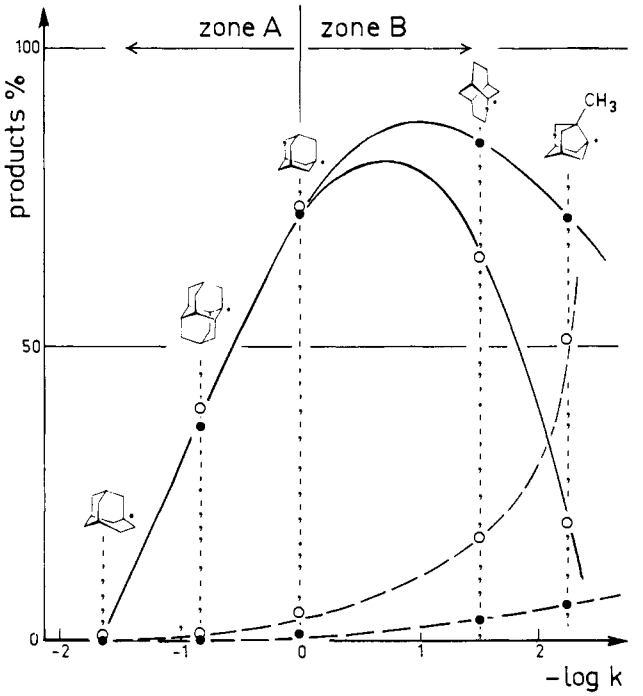


Figure 1. Barbier synthesis—temperature and radical stability effects of cage-structure radicals: (—) Yield of condensation alcohol; (- - -) yield of organolithium compound; (○) at −45 °C; (●) at −20 °C.

Table V. Synthesis and Reaction of Various Cage-Structure Organolithium Compounds with Adamantanone

	RBr				
	4b	5b	3b	6b	7b
% RLi, −45 °C[a,b]	0	55	75	80	81
% alcohol,[a] −20 °C	0	25	0	70	70
−45 °C	0	25	0	68	62

[a] Yields are calculated with respect to the halogenated derivative. [b] As for 1-adamantyllithium, tests indicate that these lithium compounds are stable in ether at both temperatures throughout the Barbier reactions.

lithium compound and of pinacol increase (Table III). Since at −20 °C **3b** has no organometallic pathway, it is likely that in zone A (Figure 1) only the radical pathway yields alcohol, whereas in zone B this radical pathway is in growing competition with the organometallic pathway.

The existence of this organometallic pathway is confirmed by the presence in the reaction medium, of an organolithium compound whose concentration increases when the stability of the radical decreases and when the temperature goes down. There are two possible sources for the presence of this residual lithium compound in the medium: (1) the condensation of lithium compounds on the ketone might be completely hindered, as for **3a**, in which case one would find the lithium compound that has not reacted and the pinacol resulting from duplication of the ketone; (2) there might be kinetic competition between the rate of pinacolization of the ketone and the rate of condensation of the lithium compound with this ketone, in which case a decrease in temperature would be unfavorable to the latter reaction.

A study of condensation between the various cage-structure organolithium compounds and **2** at −20 and −45 °C (Table V) indicates that at low temperature condensation is not inhibited. It therefore seems that the second possibility (i.e., kinetic competition between pinacolization and condensation of the lithium compound with ketone via the organometallic pathway) is the likely source of the residual lithium compound that forms in the Barbier reaction. The absence of residual lithium compound for the radicals in zone A (Figure 1) could be simply explained by the fact that there can be no competition between the radical and organometallic pathways since the latter does not exist. In this

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(35) It is likely that a decrease in temperature does not favor the attack on the solvent by the transitory species (R·X⁻ or R··Li) and therefore causes an increase in the surface reactions, i.e., formation of alcohol via the radical pathway (as with diamantane) or of the organometallic compounds (as with adamantane, for which there is a 1% yield of residual lithium compound at −20 °C, a 6% yield at −45 °C, and an 11% yield at −65 °C; cf. Table II).

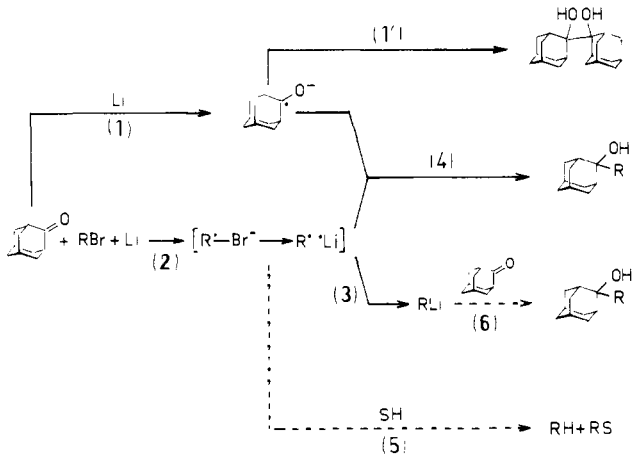

Figure 2. Reaction distribution in Barbier synthesis: (---) reaction in medium; (—) reaction at metal surface.

zone where the cage radicals are more stable than adamantyl radical, the formation of condensation alcohol via only the radical pathway could account for yields being practically unaffected by temperature.

The presence of pinacol among the end products (Figure 2) indicates the transitory formation of a ketyl radical by transfer of a single electron between the metal and the ketone (1), since, as we confirmed, no pinacol forms in the absence of the metal. These duplicative reactions are known to be surface reactions with low activation energies.[36] If the attack on the metal by a halogenated derivative is also expressed by the transfer of a single electron, at the metal–solution interface, between the lithium and the halogenated derivative (2) then 2 low activation energy reactions must occur at the metal surface, pinacolization and attack of the metal by the halide. While at −20 °C the yield is not nil, at −45 °C it is either barely affected or completely unaffected.

In contrast, addition of the lithium compound to the ketone involves a high activation energy (10 kcal/mol) and takes place in the reaction medium (6). Therefore, the radical pathway (4) that is barely sensitive to temperature can only be understood in terms of a surface reaction involving the attack by the ketyl radical on the anion radical or pair of radicals (R··Li) before formation of the organometallic compound.

The stability of the cage radical that conditions the lifespan of the precursors of the organolithium compound (R÷X⁻ or R··Li) must also affect the degree of adsorption of these transitory spacies at the metal surface.[37] Thus, for the most stable cage radical resulting from the attack on lithium by **4b**, the very slight degree of adsorption of the corresponding transitory species is unfavorable to the subsequent reactions occuring at the metal surface, i.e., generation of the lithium compound (3) and formation of alcohol via the radical pathway (4). In this case, the principal behavior of these species would be to diffuse in the reaction medium and react with the solvent, thereby yielding mostly the reduction hydrocarbon RH and solvent derivative RS[37] (5). As for the ketone, it would react with the metal and yield a ketyl radical (1) that, since it cannot react with any other entity at the metal surface, would duplicate into pinacol (1').

As the stability of the radical decreases, the degree of adsorption of the transitory species at the metal surface increases, thereby favoring the surface reactions involving these species. Because of this, the attacks on the solvent (5) are in growing competition with the radical pathway (4) leading to the condensation alcohol, and this competition continues up to and including the adamantyl radical for which the 71% yield of alcohol forms only via the radical pathway. Beyong this adamantyl radical, for twistane and methylnoradamantane, the degree of adsorption of the transitory species continues to grow with the instability of the cage radicals and favors the surface reactions to an even greater extent.

Among these latter surface reactions, the decrease in radical stability enhances the organometallic pathway (3) over the radical pathway (4), as more and more lithium compound is observed in the medium. Since the rate of formation of the ketyl radical (1), which is not dependent on the nature of the cage radical, is constant, such a result indicates that the greater the increase in the degree of adsorption of the transitory species at the metal surface, the greater the tendency of these species to give the organolithium compound. However, at the low temperatures at which we have been working, the subsequent step of condensation between the organolithium compound with the ketone (6) is greatly delayed, so that the kinetic competition between (6) and duplication of the ketone (1') favors this latter reaction, and the lithium compound accumulates in the medium. Thus, for these cage-structure compounds the yield of alcohol decreases, whereas the amount of pinacol formed increases as the stability of cage radicals decreases.

Conclusions

The study described indicates that **3a** does not react with **1** or with **2** in ether at −20 °C to yield the expected condensation alcohols. However, under the same conditions, a solution of **3b** and ketone in the presence of a slight excess of lithium powder generates good yields of the corresponding alcohol. These results unambiguously demonstrate that the Barbier reaction can occur without the in situ formation of the organometallic compound. It seems highly likely that this mechanism results from the reaction between the ketyl radicals and the transitory species (R÷X⁻ or R··Li) of the organometallic compound before its formation.

By extending this study to other cage structures homologous to adamantane, it has been possible to demonstrate that this radical pathway can be in competition with the organometallic pathway and that one of the factors that regulate this competition is the stability of the cage radical. Thus, when the lifespan of this radical decreases, the organometallic pathway is favored over the radical pathway, and vice versa.

The fact that the one-step Barbier reaction quite often results in greater yields than the two-step Grignard reaction underscores the interest of this study. Indeed, from knowledge of the radical stabilities of various structures, the reaction yield can be optimized by choosing wisely between the Grignard reaction and Barbier synthesis.

Experimental Section

Melting points were determined with a Mettler FP5 apparatus. Infrared spectra were recorded on a Perkin-Elmer Model 225 infrared spectrophotometer. Nuclear magnetic resonance spectra were recorded on a JEOL C-60 HL spectrometer with tetramethylsilane as an internal standard. Mass spectrometric data were obtained with a JEOL JMS 200 spectrometer connected to a JEOL Gas 20 K GLC and a JEOL mass data system computer. Gas chromatographic analyses were performed on an Intersmatt IGC 12 DFL instrument fitted with a Carbowax 20M or an SE 30 gas chromatography column at different temperatures. Merck alumina (Neutral Grade II) was used for liquid column chromatography; petroleum ether (30–60 °C), CCl_4, and ethyl ether were used for product purification.

1-Bromoadamantane. Adamantane (244 g) (Aldrich, Gold Label) was treated with 310 mL of bromine by the method of Landa or Stetter.[38,39] The resulting crude product was recrystallized from ethyl acetate and yielded 265 g of white solid: mp 119.5 °C (lit. mp 119.5–120 °C,[38] 118 °C[39]).

1-Adamantanol. 1-Bromoadamantane was converted quantitatively to 1-adamantanol: mp 288 °C (lit. mp 288.5–290 °C,[38] 282 °C[40]) by the solvolytic methods.[38,40]

1-Chloroadamantane. 1-Adamantanol (20 g) was treated with a mixture of thionyl chloride (25 mL) and CCl_4 (60 mL), using the procedure of Stetter.[40] Recrystallization from methanol yielded 20.5 g white solid: mp 166 °C (lit.[40] mp 165 °C).

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1-Bromodiamantane. Diamantane (20 g) prepared by the literature method[41-47] was treated with 100 mL of bromine. The resulting crude product was recrystallized from ethyl acetate and yielded 21 g of 1-bromodiamantane: mp 218 °C (lit.[48,49] mp 222–224 °C).

3-Bromohomoadamantane. Under an argon atmosphere anhydrous dichloromethane (25 mL) and 3-homoadamantanol (5 g), prepared by the method of Stetter,[50] were introduced into a 200-mL Erlenmeyer flask. To this a solution of freshly distilled thionyl bromide (6 mL) in dichloromethane (50 mL) was slowly added, and the overall contents were then refluxed for 3 h. When all the alcohol had transformed, the solution was diluted with water and extracted by CH_2Cl_2. The organic phase was then washed with water, neutralized with bicarbonate, and dried with sodium sulfate. It was then filtered and evaporated to yield 6.5 g of a yellow product that was recrystallized in methanol and yielded 5.5 g of a white product: mp 124 °C (lit.[50] mp 124.5–125.5 °C).

An original method devised in this laboratory for synthesizing 3-bromohomoadamantane from hydroxymethyl adamantane ($AdCH_2OH$) was also used. Under an argon atmosphere and at room temperature, 3 g of PBr_5, 10 mL of benzene and 1 g of $AdCH_2OH$[40] were added together in a 50-mL Erlenmeyer flask, and the solution was then stirred for 1 h. After carefully diluting it with water, the solution was extracted with pentane. The organic phase was then washed in water, dried with sodium sulfate, and evaporated to dryness to yield 1.4 g of a whitish product, 90% of which was 3-bromohomoadamantane and 10% of which was (bromomethyl)adamantane ($AdCH_2Br$). This product was then recrystallized in methanol to yield a product identified by NMR and mass spectroscopy as 3-bromohomoadamantane.

1-Bromotwistane. By treatment of 3 g of 1-twistanol, prepared by the method of Deslongchamps,[51,52] with 10 mL of freshly distilled thionyl bromide a crude product was obtained that was then purified by liquid column chromatography (LCC) with alumina. This yielded 3.9 g of 1-bromotwistane: mp 126 °C (lit.[53] mp 125–127 °C).

7-Methyl-3-noradamantanol. Into a three-necked Morton flask equipped with an argon inlet, a dropping funnel, a Hershberg stirrer, and a cooler were added 45 g of 7-*exo*-methylenebicyclo[3.3.1]nonan-3-one,[54] 1 L of anhydrous ether, and 10 g of sodium cut into small pieces. Then, while the solution was undergoing vigorous stirring, water was added dropwise so as to maintain a slight reflux of ether. Water addition was halted after 5 h, but stirring was continued for 2 more h.

The ethereal phase was recovered, and the aqueous phase was extracted with ether several times. All ethereal extracts were collected and washed with 5% HCl and then with water until neutralized. After drying with sodium sulfate and filtration, the solution was evaporated to dryness to yield 43 g of white product, which, after recrystallization in ethyl acetate, yielded 37 g of 7-methyl-3-hydroxynoradamantane, whose GLC purity was 99% (i.e., an 81% yield); mp 165 °C (lit.[55] mp 165–166 °C).

7-Methyl-3-bromonoradamantane. Under an argon atmosphere, 25 mL of anhydrous dichloromethane, 4 g of 7-methyl-3-noradamantanol, and a solution of 6 mL of thionyl bromide in 50 mL of CH_2Cl_2 were placed in a 200-mL Erlenmeyer flask. The reaction mixture was heated under reflux for 3 h. The solution was diluted with water and neutralized with sodium bisulfite. The organic phase was then washed with water until neutralization, dried with sodium sulfate, filtered, and dried under vacuum. The crude product was then purified by LCC. Elution with pentane yielded 4.2 g of 7-methyl-3-bromonoradamantane, whose GLC purity was 99.8% (77% yield of pure product); mp 126 °C.

Experimental Procedures Used in Grignard and Barbier Syntheses. Lithium (Alfa) was a 2% sodium alloy. This metal was degreased with a Soxlhet apparatus. Hexamethylacetone and adamantanone were from Aldrich. Ethyl ether was dried with $CaCl_2$, distilled with potassium, and placed on sodium wire while shielded from light.

Grignard Reaction. A 125-mL, three-necked Morton flask equipped with a Hershberg stirrer and containing crushed glass was cooled to −50 °C under a heavy argon stream. Once cooled to this temperature, the argon stream was diminished and 0.024 mol of lithium powder and 10 mL of anhydrous ethyl ether were introduced into this flask. After 10 min of vigorous stirring, 0.004 mol of halide (RBr) dissolved in 10 mL of dry ether was added dropwise for 30 min, during which vigorous stirring was continued. Fifteen minutes after this addition, a deuterolysis sample was removed and analyzed by GLC and mass spectrometry to determine the yield of lithium compound. Crystallized adamantanone (0.005 mol) then added was with stirring to the three-necked flask, which had remained at −50 °C. After 30 min of stirring, the cooling bath was removed and 10 mL of water was slowly added to the medium. The medium was then decanted, and the aqueous phase was twice extracted with CCl_4. The organic phases were collected and dried with sodium sulfate. The yields of condensation alcohol were determined by GLC with a 3 ft × $^1/_8$ in. SE 30 column, (oven initially at 80 °C, set to start 100 s later and than to rise 10 °C/min. up to 200 °C; injector temperature 180 °C; flame ionization detector 330 °C; nitrogen flow, 25 mL/min.).

Barbier Synthesis. Pieces of broken glass and 0.016 mol of lithium powder were introduced into a 125-mL, three-necked Morton flask. The temperature of the cooling bath was progressively lowered to −25 °C. Under a slight argon stream, 10 mL of dry ether was then added. After vigorous stirring of the medium for 15 min, a mixture of 4 mmol of the brominated derivative and 5 mmol of adamantanone in 10 mL of dry ether was added over a period of 30 min, while the medium continued to be vigorously stirred. Five minutes after addition was over deuterolysis was performed. After decanting, the medium was extracted with CCl_4. The organic phase was neutralized, dried with sodium sulfate, and subjected to GLC and mass spectrometric analysis to determine the percentage of the various components.

Purification of Condensation Alcohols. All condensation alcohols were purified by LCC with a substrate–alumina (Merck II–III, granulometry 0.063–0.200 mm) ratio that varied from 1/50 to 1/100. Elution was started with petroleum ether, continued with mixtures of petroleum ether and carbon tetrachloride, and concluded with pure carbon tetrachloride. When purity, determined by GLC, was 97%, the resulting crystals were recrystallized in methanol.

Characteristics of Alcohol Yields. (1-Adamantyl)di-*tert*-butylcarbinol: mp 105–105.5 °C; IR (CCl_4) 3622 (OH); ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 18, *t*-Bu), 1.69 (br, 6, Ad), 2–2.3 (br, 10, OH + Ad); mass spectrum (10 eV), *m/e* (relative intensity) 221 (2.4, M^+ – *t*-Bu), 135 (100, Ad^+), 87 (17.4, *t*-BuCHOH$^+$), 57 (23.3 (*t*-Bu$^+$). Anal. ($C_{19}H_{34}O$) C, H.

2-(1-Adamantyl)-2-adamantanol: mp 215 °C (lit.[56] mp 214 °C); IR (CCl_4) 3625 (OH); ^{1}H NMR ($CDCl_3$) δ 1.4 (s, 1, OH), 1.75 (s, 12 H), 9.9 (s, 10 H), 2–2.5 (br, 5 H); mass spectrum (75 eV), *m/e* 268 (2.2, $M^+ - H_2O$), 151 (29.5, Ad–OH$^+$), 150 (100, AdO), 135 (12, Ad^+). Anal. ($C_{20}H_{30}O$) C, H.

2-(1-Twistyl)-2-adamantanol: mp 160 °C; IR (CCl_4) δ 3620 (OH); ^{1}H NMR (CCl_4) δ 1.0, (s, 1, OH), 1.2–2.4 (m, 29 H); mass spectrum (20 eV), *m/e* 268 (10, $M^+ - H_2O$), 151 (36, AdOH$^+$), 150 (100, AdO), 135 (13, Tw^+). Anal. ($C_{20}H_{30}O$) C, H.

2-(1-Diamantyl)-2-adamantanol: mp 179 °C; IR (CCl_4) 3620 (OH); ^{1}H NMR ($CDCl_3$) δ 1.4 (s, 1, OH), 1.7 (s, 24 H), 2.1–2.6, (br, 9 H); mass spectrum (75 eV), *m/e* 320 (53.6, $M^+ - H_2O$) 187 (100, DA^+). Anal. ($C_{24}H_{34}O$) C, H.

2-(1-Protoadamantyl)-2-adamantanol:[57] mp 108–110 °C; IR (KBr) 3622, 3648 (OH); ^{1}H NMR (CCl_4) δ 1.2–1.5 (s, 5 H with OH 1.43), 1.6 (s, 8 H), 2.24 (s, 10 H), 2.44 (s, 3 H); mass spectrum (20 eV), *m/e* 268 (30 $M^+ - H_2O$), 135 (7.2), 93 (100). Anal. ($C_{20}H_{30}O$) C, H.

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Registry No. 1, 815-24-7; **2**, 700-58-3; **3a**, 3732-30-7; **3b**, 768-90-1; **3c**, 935-56-8; **4b**, 14504-84-8; **5b**, 30545-17-6; **6b**, 31297-35-5; **7b**,

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(57) This alcohol was unexpected, and results from rearrangement of 2-(7-methylnoradamant-3-yl)-2-adamantanol.

61898-33-7; 1-adamantanol, 768-95-6; diamantane, 2292-79-7; 1-twistanol, 22635-86-5; 7-methyl-3-noradamantanol, 1905-16-4; 7-methylenebicyclo[3.3.1]nonan-3-one, 17933-29-8; (1-adamantyl)di-*tert*-butylcarbinol, 66951-98-2; 2-(1-adamantyl)-2-adamantanol, 38172-65-5; 2-(1-twistyl)-2-adamantanol, 81476-16-6; 2-(1-diamantyl)-2-adamantanol, 69261-63-8; 2-(1-protoadamantyl)-2-adamantanol, 81476-17-7; adamantane, 281-23-2; 3-homoadamantane radical, 56263-72-0; 1-diamantane radical, 81476-18-8; 1-adamantane radical, 2819-03-6; 1-twistane radical, 56263-74-2; 7-methyl-3-noradamantane radical, 81476-19-9.

Methylal Hydrolysis: Reversal Reactions under Dilatometric Conditions and Invalidity of the Dilatometric Method

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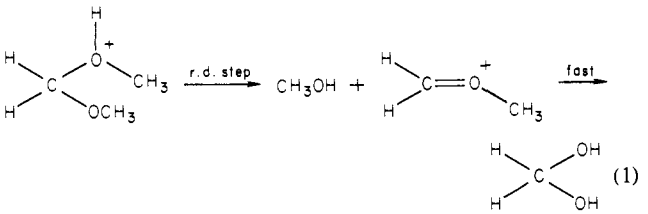
Abstract: It has been found that serious kinetic complications render the standard dilatometric method of determining rate constants of methylal hydrolysis invalid and hence becloud interpretation of the H_0 dependence of the reaction. In 0.37–3.2 M hydrochloric acid under dilatometric conditions (0.2 M in initial methylal) both the composition of the product state and the acidity of the medium change substantially during a kinetic run. As established by NMR experiments, hemiacetal as well as formaldehyde hydrate is produced, and the former in increasing proportion during a kinetic run, up to 20% at the end of hydrolysis. The downward drift effect with time that this exerts on the apparent first-order dilatometric rate constant is counterbalanced in large part by an upward drift effect exerted by a considerable increase in the acidity of the medium during a run, by −0.09 to −0.11 H_0 units. A small amount of exchange between CD_3OH and methylal during hydrolysis was observed, indicating that under dilatometric conditions some reversal of the step of oxocarbonium ion formation occurs despite the abundance of water.

As illustrated in eq 1 for dimethylformal (methylal) the accepted mechanism for acetal and ketal hydrolysis is A-1, i.e., the rate-determining step is nucleophile-unassisted heterolysis of the carbonyl carbon to oxygen bond of the reversibly formed substrate conjugate acid. The conclusion is based on a wide variety and a great number of observations (for reviews, see ref 1).



(1)

The preferred method for following hydrolysis rates of alkyl acetals of formaldehyde has been the dilatometric one.[2-4] Analytical methods of assaying formaldehyde production were cumbersome and lacked reproducibility.[3] An ultraviolet spectrophotometric method cannot be used on alkyl acetals of formaldehyde since formaldehyde is extensively hydrated in water solution.

Unfortunately, the dilatometric method requires that a high concentration of acetal be employed, typically 0.20–0.25 M,[2-4] in order that a sufficient volume change accompany the hydrolysis reaction. A volume change per se signals a change in the medium during reaction, and this could significantly affect the kinetics of a reaction, particularly one involving ions. Our suspicions were further aroused by finding that the Guggenheim method was generally employed to evaluate rate constants.[5] Since the Guggenheim method extrapolates in the limit to a two-point method of defining a line, deviations from first-order kinetics are obscured. Our view that the rate constants obtained by the dilatometric method might be unreliable was confirmed upon reading that the rate constant obtained in the hydrolysis of 0.2 M diethylformal in 0.5 M hydrochloric acid was 8% larger than that obtained when the same solution was recharged with 0.2 M diethylformal.[2] It occurred to us that the concentration dependence of the hydrolysis rate constant might be due to the alcohol being formed in sufficient amount during the hydrolysis to begin to compete with water in capturing the intermediate oxocarbonium ion, that is, that some reversal of the second step of eq 1 may be occurring, rendering the process no longer exclusively A-1 and first order. With this possibility in mind, we set out to examine the behavior of methylal in dilatometric concentrations in 0.37–3.21 M hydrochloric acid, only to find other serious kinetic complications as well.

Experimental Section

Dilatometric Kinetics. The apparatus and conditions were similar to those of Long and McIntyre.[3] The dilatometers, volume about 60 mL, had one 0.5-mm precision-bore capillary and were fitted with a high-vacuum stopcock. The reaction solution, 0.20 M in methylal, was pressured into the dilatometer from a reservoir in the constant-temperature bath. Temperature was maintained at 25 ± 0.01 °C, uniform throughout the bath. The cathetometer readings of the meniscus heights, h, were corrected for small temperature fluctuations by simultaneous readings on an adjacent dilatometer, calibrated against the first and containing only the reaction solvent. Corrections thus made were less than 2% for each reading. Readings of h were duplicatable to ±0.003 in., and the h decrease for total reaction was about 4 in. Readings were begun within 2.5 min of mixing of the reaction solutions, but only readings taken at greater than 5 min, to allow attainment of physical equilibrium, were considered significant. Usually, 15–20 readings per half-life were taken. Readings of h_∞ were stable for many half-lives beyond 10.

Exchange Experiment. A 200-mL solution of methylal (0.208 M) and CD_3OH (0.028 M) in 2.5 M hydrochloric acid was maintained at 25 °C for approximately 1 half-life of the hydrolysis. The solution was cooled,

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