A Fresh Look at Electron Transfer in the Reactions of Grignard Reagents

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Abstract: The kinetics governing product distributions in the reaction of Grignard reagents with aryl ketones have been analyzed assuming electron transfer (ET) leads to freely diffusing ketyl and alkyl radicals. The analysis shows that high yields of normal addition products are possible without assuming significant reaction within the solvent cage, but that yields of normal addition products and pinacols can vary widely depending on the rate constant for ketyl–radical coupling and the experimental conditions. The calculations are in general agreement with the literature data and remove the need for assumptions about long-lived cage processes. They also suggest new experimental approaches to the ET problem. It is concluded that the high yields of pinacols formed in the presence of small amounts of transition metals are not the result of accelerated electron transfer, but involve an alternate path for ketone reduction to ketyls.

The addition of Grignard reagents to ketones and, in general, nucleophilic additions to organometallics to electrophilic unsaturated centers play a crucial role in synthetic organic chemistry, but the kinetics and mechanisms of these reactions are clearly complex and remain subjects of continued investigation. Since excellent reviews by two of the major contributors, Ashby[1,2] and Holm,[3] are available, I shall just summarize the situation and cite specific recent papers as needed.

To begin with, solutions of Grignard reagents are complex mixtures with compositions governed by the Schlenk equilibrium

$$2RMgX \rightleftarrows R_2Mg + MgX_2 \qquad (1)$$

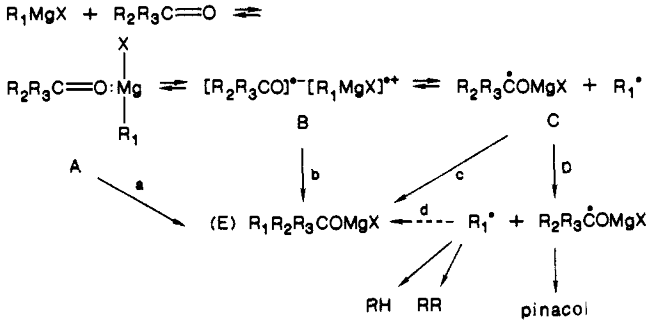
in which each component may be complexed with ether, ketone, or products of prior reaction and may associate to dimeric or polymeric forms. Heroic efforts have been made to sort these matters out, particularly by Ashby,[1,2] and the general conclusion is that, while the observed reaction rate in any particular system is first order in Grignard reagent and in ketone, rate constants for reaction of individual species present very widely.[1-3]

Conventionally, Grignard reactions have been treated as simple nucleophilic additions, but there is now extensive and convincing evidence that in additions to aromatic ketones, some, at least, of the reactions occur via electron transfer (ET). This evidence includes variation of rates with structure and sensitivity to transition-metal impurities in the Mg, direct detection of ketyls in the reaction solutions and formation of dimeric products (pinacols), ring substitution (1,4- and 1,6-addition) to the ketone, and typical radical rearrangements of the alkyl group derived from the Grignard reagent.

Two important questions arise. Is ET the sole reaction path, or a minor side process? Are the final products of these ET processes formed within the initial solvent cage, or do they involve freely diffusing species? Most investigators have formulated the reaction along the lines of Scheme I. Here A represents an initial ketone–Grignard complex, B a radical cation–radical anion pair, C a Mg ketyl–radical pair still in the solvent cage, and D a freely diffusing ketyl and radical. The normal addition product, E, is thought to arise chiefly from the caged species A, B, and C, while the "escaped" species D produces side products.

While there is some evidence supporting this scheme (see below), I think it has serious difficulties. First, the operational difference between path a (simple nucleophilic addition) and b and how their transition states would actually differ is hard to make out, and since ET is energetically uphill, little B should be present. Second, since there are no obvious forces holding R• and ketyl together, C must have a very short life, and for path c to contribute much product, it must require a very large rate constant for R•–ketyl coupling. Such a high rate constant, however, is inconsistent with the significant amounts of radical rearrangements which have sometimes been observed, e.g. in the reaction of 1,1-dimethyl-5-hexenylmagnesium bromide with benzophenones where addition products are largely cyclized.[4]

Scheme I



Path d, formation of addition product from freely diffusing radicals and ketyls, has generally been discounted, since it appears to require a selective cross-coupling of R• and ketyl in competition with the many other fast reactions which R•'s might be expected to undergo. However, in an elegant analysis Fischer[5] has shown that in a system in which two radicals are generated, one of which (here the ketyl) is persistent and only disappears by cross-reaction, while the other (here R•) can disappear by cross-reaction and a number of other paths, the former will quickly build up in concentration to the point where cross-reaction becomes the dominant fate of both species.

With this in mind, I here present kinetic analysis of the ET reaction, assuming that essentially all products arise from freely diffusing ketyl and R• species, and show that results assuming plausible rate constants are in qualitative agreement with experimental data. Further, in any given system it turns out that product distributions should be surprisingly dependent on such factors as concentration and rates of reagent addition, suggesting some new experimental approaches to studying ET processes and optimizing yields in synthetic procedures.

I take the gross rate of the RMgX–ketone reaction as V, with a fraction, F, occurring through cage reactions a, b, c (here not distinguished). Accordingly, the rate of production of ketyl ($K^{\bullet-}$) and R• is $(1 - F)V$. R•'s disappear by reaction with $K^{\bullet-}$

$$R^\bullet + K^{\bullet-} \xrightarrow{k_2} RK\ (=R_1R_2R_3COMgX) \qquad (2)$$

by bimolecular reaction with each other

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[1] Ashby, E. C.; Laemmle, J.; Neumann, H. M. *Acc. Chem. Res.* **1974**, *7*, 272.

[2] Ashby, E. C. *Pure Appl. Chem.* **1980**, *52*, 545.

[3] Holm, T. *Acta Chem. Scand., Ser. B* **1983**, *B37*, 569.

[4] Ashby, E. C.; Bowers, J. R., Jr. *J. Am. Chem. Soc.* **1981**, *103*, 2242.

[5] Fischer, H. *J. Am. Chem. Soc.* **1986**, *108*, 3925.

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$$2\mathrm{R}^{\bullet} \xrightarrow{2k_3} \mathrm{R{-}R} \qquad (3)$$

by attack on solvent SH ([SH] will be taken as unity)

$$\mathrm{R}^{\bullet} + \mathrm{SH} \xrightarrow{k_4} \mathrm{RH} + \mathrm{S}^{\bullet} \qquad (4)$$

and may also rearrange

$$\mathrm{R}^{\bullet} \xrightarrow{k_5} \mathrm{R}^{\bullet\prime} \qquad (5)$$

For simplicity, I take the k's for reaction of $\mathrm{R}^{\bullet}$, $\mathrm{R}^{\bullet\prime}$, and $\mathrm{S}^{\bullet}$ as being the same, so their concentrations may be combined (eq 6).

$$\mathrm{R_t}^{\bullet} = \mathrm{R}^{\bullet} + \mathrm{R}^{\bullet\prime} + \mathrm{S}^{\bullet} \qquad (6)$$

Ketyl, in turn, disappears via reaction (2), but I shall also consider its reversible dimerization to an inactive species, presumably the magnesium pinacolate

$$2\mathrm{K}^{\bullet-} \overset{K_{\mathrm{ket}}}{\rightleftarrows} \mathrm{D} \qquad (7)$$

so that free ketyl is given by

$$[\mathrm{K}^{\bullet-}]_{\mathrm{f}} = [(1 + 8K_{\mathrm{ket}}[\mathrm{K}^{\bullet-}]_{\mathrm{t}})^{1/2} - 1]/2K_{\mathrm{ket}} \qquad (8)$$

with these assumptions:[6]

$$\mathrm{d}[\mathrm{R_t}^{\bullet}]/\mathrm{d}t = (1 - F)V - k_2[\mathrm{R_t}^{\bullet}][\mathrm{K}^{\bullet-}]_{\mathrm{f}} - 2k_3[\mathrm{R_t}^{\bullet}]^2 \qquad (9)$$

and

$$\mathrm{d}[\mathrm{K}^{\bullet-}]/\mathrm{d}t = (1 - F)V - k_2[\mathrm{R_t}^{\bullet}][\mathrm{K}^{\bullet-}]_{\mathrm{f}} \qquad (10)$$

Except at very early stages in the reaction, the steady-state assumption for $[\mathrm{R_t}^{\bullet}]$ may be introduced, setting $\mathrm{d}[\mathrm{R_t}^{\bullet}]/\mathrm{d}t = 0$ in (9) and yielding

$$[\mathrm{R_t}^{\bullet}] = [(k_2[\mathrm{K}^{\bullet-}]_{\mathrm{f}}/2k_3)^2 + 2(1 - F)V/k_3]^{1/2} - k_2[\mathrm{K}^{\bullet-}]_{\mathrm{f}}/2k_3 \qquad (11)$$

Three other quantities are of interest. First, the rate of possible rearrangement of $\mathrm{R}^{\bullet}$ (eq 12) (leading to $\mathrm{R}^{\bullet\prime}$ containing products), i.e. the rate of formation of $\mathrm{R}^{\bullet}$ multiplied by the fraction of $\mathrm{R}^{\bullet}$'s which rearrange

$$\mathrm{d}[\mathrm{R}^{\bullet\prime}]/\mathrm{d}t = (1 - F)Vk_5/(k_2[\mathrm{K}^{\bullet-}]_{\mathrm{f}} + k_3[\mathrm{R_t}^{\bullet}] + k_4 + k_5) \qquad (12)$$

Second, the rate of formation of RK (eq 13) (including both $\mathrm{R}^{\bullet}$ and $\mathrm{R}^{\bullet\prime}$ units).

$$\mathrm{d}[\mathrm{RK}]/\mathrm{d}t = (1 - F)Vk_2[\mathrm{K}^{\bullet-}]_{\mathrm{f}}/(k_2[\mathrm{K}^{\bullet-}]_{\mathrm{f}} + k_3[\mathrm{R_t}^{\bullet}] + k_4) \qquad (13)$$

Third, the rate of formation of RH (eq 14) (again including $\mathrm{R}^{\bullet}$ and $\mathrm{R}^{\bullet\prime}$).

$$\mathrm{d}[\mathrm{RH}]/\mathrm{d}t = (1 - F)Vk_4/(k_2[\mathrm{K}^{\bullet-}]_{\mathrm{f}} + k_3[\mathrm{R_t}^{\bullet}] + k_4) \qquad (14)$$

Actual yields of ketyl, RK, and RH may now be obtained by numerical integration of these differential equations for selected values of V, k's, F, and K_{ket}.

First, I consider a reaction run under typical large-scale synthetic conditions: slow addition of one component to a solution of the other so that V is constant. Taking $V = 10^{-4}$ M s^{-1} and $t = 1000$ s (corresponding to addition of a 0.1 mol of one component to a 1-L solution of an equivalent (or excess) of the other over about 17 min) and setting F and K_{ket} as zero (i.e., no cage reaction or ketyl dimerization), I choose plausible k values as follows (the units are M and s): $k_3 = 2 \times 10^9$ (a typical value for alkyl radical dimerization), $k_4 = 200$,[7] and $k_5 = 10^5$ (typical for 5-hexenyl radical cyclizations).[8] A crucial parameter is k_2, and the only value available[9] is for the reaction of a primary alkyl radical with the Li ketyl of benzophenone in THF, 1.5×10^8, so my initial choice is in this range. Figure 1 shows representative plots of ketyl formation for $k_2 = 0.5$, 1, 2, and 5, all $\times 10^8$, and

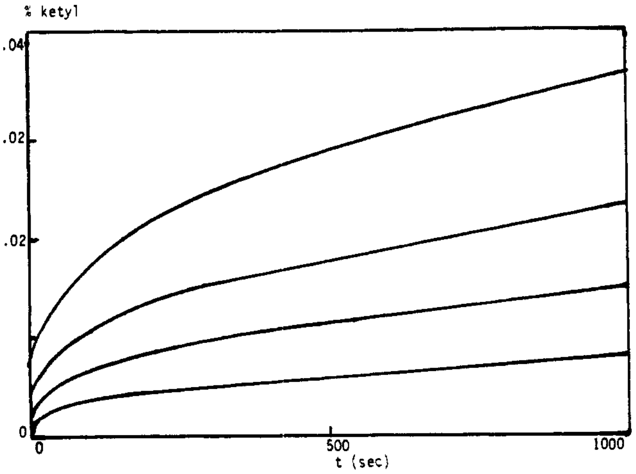

Figure 1. Calculated growth of ketyl in Grignard–ketone reaction. In ascending order, $k_2 \times 10^{-8}$: 0.5, 1, 2, and 5. Other constants are as in the text.

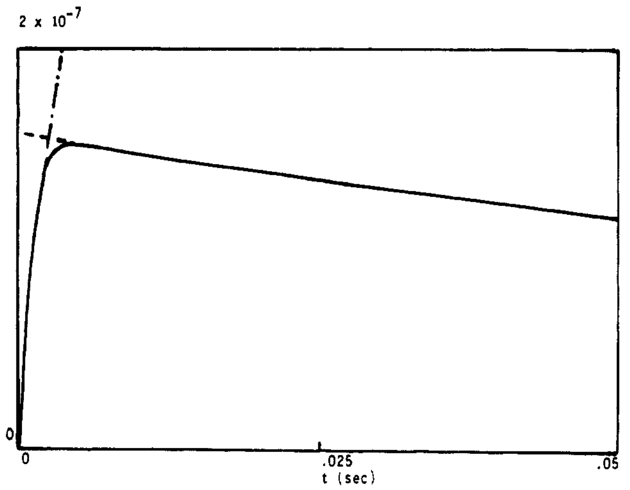

Figure 2. Calculated radical concentrations during first 0.05 s of Grignard–ketone reaction: (---) steady-state assumption, (–•–) ketyl concentration.

Table I. Calculated Product Distribution in ET Grignard–Ketone Reactions (Slow Mixing)[a]

run no.	% yield[b] K	RK	RH	rearr	notes
1	4.71	89.5	5.78	95.8	$k_2 = 10^6$
2	1.04	96.3	2.73	92.4	$k_2 = 10^7$
3	0.22	98.5	1.28	85.2	standard
4	0.05	99.3	0.60	73.3	$k_2 = 10^9$
5	3.86	96.3	5.56	96.0	$K_{\mathrm{ket}} = 10^6$
6	0.18	98.7	1.15	65.5	25% cage react.
7	0.14	98.9	1.01	45.0	50% cage react.
8	0.09	99.1	0.79	23.3	75% cage react.
9	0.31	98.7	0.96	81.2	$k_3 = 5 \times 10^9$
10	0.14	97.8	2.03	90.1	$k_3 = 10^8$
11	0.23	1.68	98.3	8.9	$k_4 = 10^6$
12	0.05	3.50	96.5	8.80	$k_2 = 10^9$, $k_4 = 10^6$
13	0.11	99.6	6.28	56.3	$V = 10^{-3}$ (more concn)
14	0.48	93.9	5.63	96.1	$V = 10^{-5}$ (less concn)
15	0.49	98.9	0.61	74.2	t = 100 (fast addn)
16	1.04	98.7	0.28	56.3	t = 10 (very fast addn)

[a] Standard conditions (see text): $V = 10^{-4}$ M/s, $t = 10^3$ s, $k_2 = 10^8$, $k_3 = 2 \times 10^9$, $k_4 = 200$, $k_5 = 10^5$, and F and $K_{\mathrm{ket}} = 0$. [b] K = ketyl, RK = addition product, RH = hydrocarbon from attack on solvent, and rearr = rearranged R's if $k_5 = 10^5$.

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[6] Garst and Smith (Garst, J. F.; Smith, C. D. *J. Am. Chem. Soc.* **1976**, *98*, 1526) give a similar analysis of the Wittig rearrangement of benzhydryl alkyl ethers (which also give ketyl–radical pairs) but do not examine the consequences in the detail given here.

[7] This value was based on an extrapolation of gas-phase data for the reaction of methyl radicals with THF. Recently liquid-phase values of 2000 and 6000 have been reported for the reaction of tertiary and primary radicals with THF at 50 °C, so 200 may be low. However, RH is, in any case, a minor product; cf.: Newcomb, M.; Park, S. U. *J. Am. Chem. Soc.* **1986**, *108*, 4132.

[8] Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317.

[9] Garst, J. F.; Smith, C. D. *J. Am. Chem. Soc.* **1976**, *98*, 1520.

indicate final yields of 0.07–0.4%, with most of the ketyl formed early in the reaction.

Figure 2 shows the very early stages of one of these reactions ($k_2 = 1 \times 10^8$), with the differential equation (9) to calculate [$R_t^\bullet$]. We see that [$R_t^\bullet$] quickly rises to a maximum within a few milliseconds, while [$K^{\bullet-}$] disappears off the scale. Beyond this maximum the agreement with [$R_t^\bullet$] calculated with the steady-state assumption is complete, which clearly justifies its use.

Table I shows final product distributions resulting from a series of similar calculations in which parameters were systematically varied. Runs 1–4 show that ketyl yields (which presumably would be converted to pinacols on workup) rise regularly as k_2 is decreased and also increase if significant ketyl dimerization is assumed (run 5). The value of K_{ket} chosen corresponds to 98% dimerization at the end of the reaction.

Actually, there seems to be few data on the physical state of Mg ketyls. Alkali metal ketyls readily dimerize, but in ether solvents these dimers are chiefly paramagnetic species and presumably reactive. Hirota and Weissman[10] report that the ESR spectra of Mg ketyls indicate that the paramagnetic species present are chiefly dimeric, but how much diamagnetic pinacolate is also present was not determined.

Runs 6–8 assume 25–75% cage reaction. As would be expected, yields of ketyl and rearrangement are both reduced. Here I should note that if $k_2 \leq 10^8$, very little cage reaction involving $R^\bullet$ and $K^{\bullet-}$ should be expected,[11] although a competing nucleophilic addition, path a in Scheme I, would have the same effect on kinetics and product distributions.

Runs 9 and 10 examine the effect of changes in k_3. Over a 10-fold range covering plausible values for $R^\bullet$ dimerizations, ketyl yields change by only a factor of 2.

Runs 11 and 12 consider the effect of a much more rapid reaction of $R^\bullet$'s with solvent, as would be expected with aryl Grignard reagents. Taking $k_4 = 10^6$ as an estimate,[12] we see that RH should be the chief product, rather than RK, even if k_2 is taken as 10^9. Such reactions should produce large amounts of products derived from solvent radicals. Runs 13–16 show that product distributions are also surprisingly sensitive to reagent concentrations and rates of addition, dilute systems and rapid addition rates being associated with higher ketyl yields.

This important observation becomes more significant if I consider reactions where ketone and RMgX are mixed all at once and then allowed to react, as is done in kinetic studies and, commonly, in small-scale reactions where heat dissipation is not important.

I have examined this case by simulating reactions where one reagent is quickly added to an excess of the other, and reaction then follows pseudo-first-order kinetics. Here the gross reaction rate, V, is given by

$$V = ck_1e^{-k_1t} \tag{15}$$

where k_1 is the rate constant for the gross ketone–RMgX reaction and c the product of initial concentrations of ketone and RMgX.

Figure 3 plots the course of four such reactions for varying k_1's with $c = 0.1$, corresponding to reagent concentrations of 0.1 and 1 M. Time scales are variable, so that each reaction has been followed to $t = 5/k_1$ or 99.3% reaction. We see that ketyl yields are larger than those in comparable slow-addition experiments and rise with increasing values of k_1. Further, in every case, most of the ketyl is formed within the first reaction half-life.

Table II summarizes product distributions calculated for a number of experiments carried out under these "quick-mix" conditions. Clearly, with large values of k_1 and small values of k_2, ketyls can become major reaction products.

In practice, measured rate constants vary over several powers of 10 for different systems, e.g. for benzophenone with excess Grignard rates vary from ~0.1 $M^{-1}\,s^{-1}$ for CH_3MgX to ~100 $M^{-1}\,s^{-1}$ for t-BuMgX.[3,13] The higher rates for tertiary Grignards has been one of the strong arguments for an ET process, and, from this analysis, these high rates in turn lead to larger yields of side products.

Table II. Calculated Product Distributions in ET Grignard–Ketone Reactions (Quick Mixed)[a]

		% yield			
run no.	k_1	K	RK	RH	rearr
21	100	7.79	91.5	0.03	13.6
22	10	3.77	95.5	0.07	24.7
23	1	1.78	97.4	0.14	40.6
24	0.1	0.83	98.2	0.31	58.8
25	0.01	0.39	98.3	0.65	74.9
26[b]	1	7.79	91.3	0.32	60.1
27[c]	1	28.8	70.0	0.70	77.3
28[c]	100	69.1	30.1	0.13	39.6

[a] All k values are as in Table I, footnote a, unless indicated otherwise. [b] $k_2 = 10^7$. [c] $k_2 = 10^6$.

In summary, this analysis leads to several predictions for comparison with actual experimental data and can provide the basis for further experimental work.

1. Even in reactions proceeding entirely via ET, yields of normal addition products can be almost quantitative without invoking cage processes. Yields of ketyls and other byproducts can vary widely, depending both on the value of k_2 and the gross reaction rate. Low ketyl yields, accordingly, are not, per se, evidence that only a small fraction of reaction involves ET or noncage processes.
2. Ketyl concentrations will build up rapidly early in the reaction and persist after reaction is complete.
3. High reaction rates should give higher yields of ketyls and byproducts.
4. Under most assumed conditions, radicals will have long enough lifetimes to undergo rearrangements which have rate constants of ~10^5. The calculated "rearrangement yields" in Tables I and II give a good idea of average radical lifetimes. Aliphatic radicals will have too short a life for significant attack on the solvent, but solvent attack should be important for aryl radicals.
5. Since, except for any contribution by cage processes, free $R^\bullet$'s and ketyls are produced in stoichiometric quantities, small amounts of traps for $R^\bullet$ or ketyls may have little effect on the products.

Comparison with Experiment

Qualitatively, many literature observations on reactions between Grignard reagents and aromatic ketones where there is evidence for ET are consistent with our model. Ketyls are detected early and persist. Further, yields of ketyls and side products are larger with tertiary Grignard reagents which react very rapidly than with slower reacting species, e.g. CH_3MgX. Finally, tertiary 5-hexenyl radicals show extensive cyclization, as our analysis predicts.

More quantitative comparison with individual experiments is difficult. First, values of k_2 and the importance of ketyl dimerization must be assumed. Further, reported product distributions are often incomplete and reaction rates ill-defined (in particular, with tertiary Grignard reagents which react very rapidly, it may be unclear whether mixing or reaction is rate controlling). Accordingly, I shall give only a few examples, taken chiefly from Ashby's laboratory.

The strongest experimental evidence for ET is in the reaction of tertiary Grignard reagents with aromatic ketones, and it is here too that ET is energetically most favorable since the Grignard is easily oxidized and the ketone easily reduced.[3] In one study,[4] several experiments in which 0.0333 M t-BuMgCl reacted with 0.0167 M 2-methylbenzophenone gave 7.8–11.2% pinacol on workup. Taking $k_1 = 100$, approximately Crossland and Holm's rate constant, and assuming there is no cage reaction or ketyl dimerization, a pinacol yield of 10% is predicted if $k_2 = 5 \times 10^7$.

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(10) Hirota, N.; Weissman, S. I. *J. Am. Chem. Soc.* **1964**, *86*, 2532.

(11) More specifically, the simplest model predicts that the fraction of cage reaction can be expressed as $k_r/(k_r + k_d)$, where k_r is a rate constant for reaction, and k_d a rate constant for diffusion, in ordinary solvents ~5×10^9. For $k_2 = 10^9$, this predicts 17% cage reaction; for $k = 10^8$, 2% is predicted.

(12) This is probably a conservative value. A rate constant of 4.8×10^6 for the reaction of phenyl radicals with THF has been reported: Scaiano, J. C.; Stewart, L. C. *J. Am. Chem. Soc.* **1983**, *105*, 3609.

(13) Holm, T.; Crossland, I. *Acta Chem. Scand.* **1971**, *25*, 59.

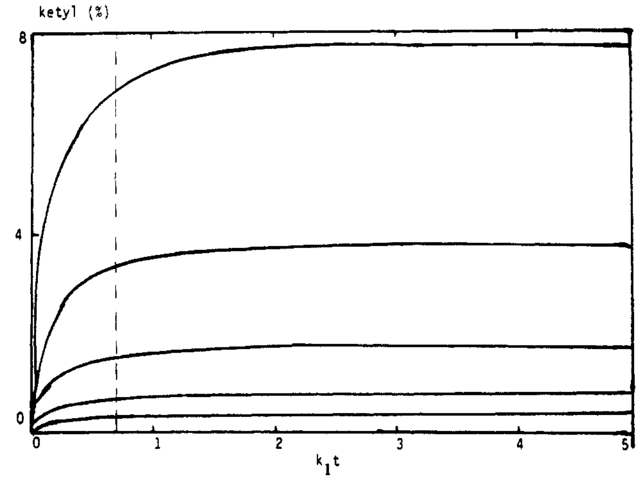

Figure 3. Calculated ketyl concentration in "quick-mix" Grignard reaction. In ascending order, k_1 = 0.01, 0.1, 1.0, 10, and 100. The dashed line marks 1 half-life. Other k values are as in Table I, footnote *a*.

Actually, there is evidence for some cage reaction in such tertiary Grignard systems. In the same paper,[4] reaction of 1,1-dimethyl-5-hexenylmagnesium chloride with benzophenone was found to give 61% 1,6- (i.e. para) addition (73% cyclized) and 39% 1,2- (i.e. normal) addition product (2% cyclized). The 73% cyclization is about that predicted in the above calculation, and the result suggests that little of the 1,6- and most of the 1,2-addition products arise from cage processes (or, for the later, a competing non-ET process). Several other experiments gave comparable results, always with more cyclization of 1,6- than 1,2-addition products, and Ashby clearly recognized the necessity for a longer lifetime for the radicals producing the 1,6-addition product. Similarly, Garst and Smith[6] have concluded that, in the Wittig rearrangement of lithiobenzhydryl 5-hexenyl ether, only 16% of the ketyl–radical pairs escape the solvent cage. Their argument is complex and the amount of escape seems low, but some cage reaction may well be involved in all the systems discussed here. However, since the amount cannot usually be estimated and my concern is with the noncage process, it has been ignored.

Two other observations on tertiary systems are pertinent. Addition of 12.5% *p*-dinitrobenzene to *t*-BuMgCl–2-methylbenzophenone systems had little effect on the ratio of 1,6- and 1,2-addition products, but eliminated the yield of pinacol. This would be consistent if the DNB had destroyed most of the ketyl in the system by the time the system was quenched, but enough was still present during the reaction to effectively trap *tert*-butyl radicals. In any case, since Grignard reagents themselves react rapidly with nitroaromatics, the reaction is complex. More significant were experiments on the same system carried out in the presence of the Mg ketyl of fluorenone. These were planned as a deliberate test for free *tert*-butyl radicals, which should have been trapped as the fluorenone addition product, but none was detected. Although various ad hoc explanations can be invented,[14] this would seem to be the most significant evidence against my analysis and certainly needs further attention.

The energetics for ET between CH_3MgBr (and other primary RMgX's) and benzophenones is less favorable and the evidence for its importance more equivocal. Although ketyls have been detected spectroscopically in CH_3MgBr reactions to benzophenones, Ashby reports that, using highly purified Mg, pinacol yields are <1%.[15,16] Recently he reported a further study[17] in which both ketyl concentrations and percent reaction were followed in the reaction between 0.66 M CH_3MgBr and 0.066 M 2-methylbenzophenone. The data gave $k_{obsd} = 6.5 \times 10^{-3}$ s^{-1} and the reaction was followed from approximately the end of the first half-life. Ketyl began to form immediately and, at one half-life, had reached a concentration of ~0.01%, more or less as indicated in the curves of Figure 3. However, thereafter it slowly declined, implying some further reaction not included in this analysis. Applying my analysis to the above data predicts 0.35% ketyl at 1 half-life if $k_2 = 10^8$ and 0.076% if $k_2 = 10^9$. Even the latter is higher than the 0.01% observed. Either ET here is only a minor side reaction or there is an implausible amount of cage reaction.

A similar experiment with phenylmagnesium bromide gave very similar results, ~0.01% ketyl, $k_{obsd} = 5.1 \times 10^{-3}$ s^{-1}, and a final yield of addition product of >92%. Since the data in Table I indicate that an ET process should have chiefly yielded benzene, these data seem even less compatible with ET, and it is conceivable that the traces of ketyl observed in both experiments arose from traces of Fe or other transition metals present (see below).

Ashby has also investigated several primary Grignard reagent reactions in his search for ET processes. 5-Hexenylmagnesium bromide shows no cyclization in addition products, while 2,2-dimethyl-5-hexenylmagnesium bromide does.[4] Similarly Blomberg and Mosher[18] have reported 20% benzopinacol in the reaction of neopentylmagnesium chloride with benzophenone. The latter two reactions are both quite slow, and both Ashby and Holm have noted that, since ET processes should be less subject to steric effects than should nucleophilic addition, ET should be favored in highly hindered systems. The high yield of benzopinacol noted by Blomberg and Mosher also suggests that, in our scheme, k_2 is reduced in hindered systems. (Additional examples appear in the next section.)

A final point remains to be discussed. In 1941 Kharasch showed that the addition of small amounts of transition-metal salts (notably Fe and Mn) to primary RMgX–benzophenone reactions led to high yields (up to 90%) of pinacol,[19] and Ashby has shown that even the traces of transition-metal impurities in different grades of Mg lead to variations in reaction rates and pinacol yields.[1,14,15] Both Kharasch and Ashby have interpreted these reactions as involving intermediate organometal and lower valence metal species which reduced ketone to ketyl and are recycled, e.g. for iron

$$\mathrm{Fe(II)} + 2\mathrm{RMgX} \rightarrow \mathrm{FeR_2} \tag{16}$$

$$\mathrm{FeR_2} \rightarrow \mathrm{Fe(0)} + \mathrm{RR} \tag{17}$$

$$\mathrm{Fe(0)} + 2\mathrm{R_2CO} \rightarrow \mathrm{Fe(II)} + 2\mathrm{R_2\dot{C}{-}O^-} \tag{18}$$

(the specific structures and oxidation states are purely illustrative and not critical). This formulation is compatible with my scheme with one important proviso: The breakdown of FeR_2 in (17) must be some sort of reductive elimination[20] and not a homolysis liberating R$^{\bullet}$'s, since they would be chiefly trapped by ketyl to give normal addition products. Thus the effect of the metal is not to facilitate the usual ET process but to provide an additional route for ketyl formation.

Reduction and Enolization

Two other side reactions, particularly important with highly hindered ketones, need to be discussed in connection with my formulation of the ET process. The first is the reaction yielding carbinol and olefin (eq 19).

$$\mathrm{R_2CO} + \mathrm{RCH_2CH_2MgX} \rightarrow \mathrm{R_2CHOMgX} + \mathrm{RCH{=}CH_2} \tag{19}$$

In the electrophilic addition model, it can be formulated as an alternative hydride transfer

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[14] For example, that fluorenone ketyl, being less sterically hindered, is more extensively dimerized, or that the benzophenone ketyl, being freshly produced with a lifetime of a fraction of a second, has not had time to associate.

[15] Ashby, E. C.; Buhler, J. D.; Lopp, J. G.; Weisemann, T. L.; Bowers, J. S., Jr.; Laemmle, J. T. *J. Am. Chem. Soc.* **1976**, *98*, 6561.

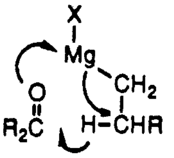
[16] Ashby, E. C.; Wiesemann, T. L. *J. Am. Chem. Soc.* **1978**, *100*, 189.

[17] Zhang, Y.; Wenderoth, B.; Su, W.-Y.; Ashby, E. C. *J. Organomet. Chem.* **1985**, *292*, 29.

[18] Blomberg, C.; Mosher, H. S. *J. Organomet. Chem.* **1968**, *13*, 519. This paper contains one of the first proposals of the ET mechanism.

[19] Kharasch, M. S.; Kleiger, S. C.; Martin, J. A.; Mayo, F. R. *J. Am. Chem. Soc.* **1941**, 63, 2305, and subsequent papers.

[20] There is evidence for reductive elimination rather than homolysis in the decomposition of some ligand-stablized Fe alkyls. Compare, e.g.: Lau, W.; Hoffman, J. C.; Kochi, J. K. *Organometallics* **1982**, *1*, 155.

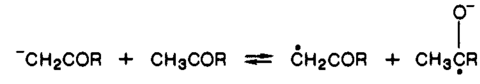


(20)

but other reaction paths have also been proposed. In 1976, Ashby reported that, with MeMgX, yields were dependent on Mg purity and suggested that here a Mg hydride was responsible for the reduction.[15] Holm[3] has suggested reductive via a disproportionation (rather than addition) reaction between radical and ketyl. In a more recent communication[21] Ashby has favored an intramolecular H transfer between a radical anion–radical cation radical pair (i.e. species B in Scheme I) analogous to reaction (20) of species A. This conclusion was based on the reactions of highly hindered dimesityl ketone with an equivalent of several aliphatic Grignards (each 0.05 M). Each system rapidly developed ketyl-like ESR and visible spectra (indicating yields of 2–80% of this species) but yielded dimesitylcarbinol much more slowly. As an example, isopropylmagnesium chloride gave 60% ketyl with a half-time of 30 min, while the carbinol yield was under 5% after a day and 20% and still rising after 12 days. Ashby's interpretation, that the spectra represented not the free ketyl but the radical–ion pair B, which then very slowly rearranged to carbinol, seems hard to accept,[22] since collapse of the radical–ion pair in less hindered cases is enormously faster and, from data discussed earlier, must be over in a fraction of a second. The scheme developed here would suggest that the spectra actually follow the rate of ketyl and radical production, and the high yield of ketyl in some cases (80% with *t*-BuMgCl, which gave no reduction product) implies a very low value for k_2 for the coupling of a bulky radical with the highly hindered ketyl.[23] If so, quenching of the isopropylmagnesium chloride reaction after 1 h should have given 60% pinacol, 40% addition products of some sort, with the remaining 60% of the isopropyl residues appearing probably as propane, propylene, and dimethylbutane. Since the electron-transfer process was over at this point, the carbinol in this case must have arisen from some further unspecified reaction of these products.

Clearly these highly hindered systems require further study, and the paths by which ketyl is slowly consumed need to be elucidated.

A final side reaction, observed with hindered ketones with α-hydrogens, is enolization. This has usually been considered a simple acid–base reaction, but could be complicated by ET between an enolate ion and an unreacted carbonyl, e.g.



$$ {}^-CH_2COR + CH_3COR \rightleftharpoons \dot{C}H_2COR + CH_3\underset{\bullet}{\overset{O^-}{\overset{|}{C}}}R \quad (21)$$

Ashby and Argyropoulos[24] have reported that the Li enolate of pinacolone and benzophenone in THF react to give a ESR active species (about 0.1% based on benzophenone) and more highly hindered ketones gave larger yields (5% for mesityl phenyl ketone). Their interest was in establishing a possible ET path for the aldol condensation (which occurs slowly in these systems), and it is worth noting that their reactions resemble the Grignard reactions just discussed in that the concentration of the ESR active, colored intermediate peaks early (before the first half-life of the aldol process) and then declines. Reaction (21) also resembles the ET Grignard process in that a persistent ketyl and a short-lived enolate radical are produced together, so that the reaction kinetics can be given the same sort of analysis as I have used here.

Conclusions

Reaction of Grignard reagents with diaryl ketones via ET to yield freely diffusing ketyl and alkyl radicals can give high yields of normal addition products, but product distributions should strongly depend on reaction conditions and k_2, the rate constant for radical–ketyl coupling.

Calculations appear in reasonable agreement with literature data, but detailed validation requires better data on actual k_2 values and the extent of dimerization of Mg ketyls. Calculations also predict a significant dependence of product distribution on concentrations and gross reaction rate, which should be amenable to experimental study.

The treatment indicates that without other evidence it is unnecessary to invoke extensive cage reaction in these systems or, in particular, ad hoc assumptions about implausibly long lifetimes for "cage" species. It also indicates that the increased formation of pinacols in the presence of traces of transition metals is not due to acceleration of ET, but must be an essentially independent process.

Finally, a similar analysis should be applicable to many of the other reactions involving carbanionic salts and substrates for which Ashby and others have obtained evidence for ET, both making claims for ET more convincing and permitting a more quantitative treatment of the results.

Note Added in Proof

Professor T. Holm has informed me that the high yields of ketyl reported by Ashby in the reactions of dimesityl ketone may have been due to Fe contamination and that, in his hands, secondary and tertiary Grignard reagents give high yields of (rather unstable) para addition products. Cf.: Holm, T. *Acta Chem. Scand., Ser. B* **1982**, *36*, 266. His data imply that k_2 for highly hindered ketyls is not, in fact, significantly slower than for benzophenone ketyl.

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[21] Ashby, E. C.; Goel, A. B. *J. Am. Chem. Soc.* **1981**, *103*, 4983.

[22] In support of his scheme, Ashby reported that different Grignard reagents gave somewhat different ESR and visible spectra with the same ketone. The interpretation here would have to assume that the different spectra arose from differing concentrations of various complexes present.

[23] Application of our analysis to the *i*-PrMgX data, assuming 30% ketyl at half reaction, implies a relatively small value for k_2, $\sim 10^4$, although dimerization at the relatively high ketyl concentrations involved would permit a larger value.

[24] Ashby, E. C.; Argyropoulos, J. N. *J. Org. Chem.* **1986**, *51*, 472.