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COMMENTARY

The Nature of Radicals Involved in Grignard Reagent Formation

My time as a graduate student with Morris Kharasch in 1937–1939 coincided with the beginning of his investigation of the effect of trace metals on the reactions of Grignard reagents.[1] My interest in the fascinating vagaries of Grignard chemistry was aroused and has continued ever since. With this background, I should like to comment on a recent controversy which has developed in the pages of this journal.[2,3]

Although the intermediacy of radicals during the formation of Grignard reagents is supported by extensive evidence and is generally accepted, the question raised is whether the Grignard reagent and the various side products produced by isomerization, attack on solvent, dimerization, etc. arise from radicals absorbed on the Mg surface, the A model,[2] or from "free" radicals diffusing freely through the solution, the D model.[3] My basis for attempting to choose between the two will be two familiar principles. First, hypotheses and models cannot be proved, they can only be "falsified" (i.e., shown to be incompatible with experiment), and the better model is the one which can be subjected to, and withstands, rigorous attempts at falsification. The second is really Occam's razor. Keep things simple.

The A model was suggested long ago by Kharasch and Reinmuth[4] and has recently been championed by Walborsky,[2] chiefly on the grounds that the distribution of side products produced during Grignard reagent formation is quite different from that observed when the same radicals are generated in homogeneous solution, and that, in some cases, Grignard reagents may be produced with significant retention of stereochemistry.

The strongest support for the D model comes from a mathematical analysis first carried out by Garst, Deutch, and Whitesides in 1986[5] and subsequently elaborated by Garst, Swift, and Smith.[6,7] While the analysis is somewhat complicated, it has the beauty that it contains only one arbitrary parameter, δ, a measure of the trapping efficiency of the Mg surface for radicals which diffuse to it; all other rate constants, e.g., for diffusion and radical isomerization, coupling, and attack on solvent, either are known from data in homogeneous solution or can be estimated or independently measured. Using a single, plausible value for δ, Garst and Swift[7] find that the model successfully predicts product distributions for a number of systems, most strikingly, for the case of Grignard formation from 5-hexenyl bromide, where yields of some five major products are successfully calculated, and six others which were not detected are predicted to be formed in only negligible quantities.

The model also provides a simple rationale for the differences in product distributions from those observed in homogeneous solution. When generated in solution, e.g., by peroxide decompositions, concentrations are $<10^{6}$ M, and lives $>10^{-4}$ s. In Grignard formation, radicals are produced in high concentration very close to the Mg surface, and most are rapidly trapped. Concentrations are thus $\sim 10^{-3}$ M, and lives $\leq 10^{-7}$ s. Their short lives decrease the extent of first-order processes such as isomerization and solvent attack, and their high concentrations favor bimolecular coupling.

This is precisely what is observed in the several examples cited by Walborsky,[2] and in some cases, the comparison can be made more quantitative. If the small amount of radical coupling is neglected, for the case where RMgX formation competes with some first-order reaction of $R^\bullet$, the D model gives a simple expression for the yield of (unaltered) RMgX, eq 1, where k is the rate constant for

$$Y = \phi\delta/(\delta + (k/D)^{1/2}) \qquad (1)$$

the first-order reaction, D is the diffusion constant for $R^\bullet$, and $\phi = \exp(-s(k/D)^{1/2})$ with s the distance of $R^\bullet$ from the Mg surface at the moment it is formed. Walborsky notes that no rearrangement is observed in the formation of neophylmagnesium chloride. The neophyl rearrangement is relatively slow ($k \sim 760$),[8] and using this value of k in

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[5] Garst, J. F.; Deutch, J. M.; Whitesides, G. M. *J. Am. Chem. Soc.* **1986**, *108*, 2490.

[6] Garst, J. F.; Swift, B. L.; Smith, D. W. *J. Am. Chem. Soc.* **1989**, *111*, 234.

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eq 1 together with Garst's values for the other parameters ($\delta = 0.01$ Å^{-1}, $D = 3 \times 10^{-5}$ cm^2/s, $s = 4$ Å) predicts 99.5% unrearranged product. Similarly, the rearrangement (1,2-shift of phenyl) of the 2,2,2-triphenylethyl radical has a much larger driving force and is reported to be complete in reactions in homogeneous solutions. Formation of the Grignard reagent from the corresponding chloride shows only 17–41% rearrangement. From eq 1 this corresponds to a k for rearrangement of 10^6–10^7, at this point a plausible value. Finally, the Grignard reagent from 1-bromo-1-methyl-2,2-diphenylcyclopropane contains about 3% of an allylic isomer in which the cyclopropyl ring has opened, implying a rate constant for the isomerization of about 3×10^4. This sort of ring opening is rarely observed at all in free-radical chemistry and here, while still slow, may derive additional driving force from conjugation of the resulting allylic radical with the two phenyl rings.

While I believe this analysis accommodates Walborsky's first argument (product distributions) quite satisfactorily, the second is more telling. Walborsky's examples of retention of stereochemistry involve vinyl and cyclopropyl halides which he has examined by a series of elegant experiments which leave little doubt about the validity of the data. For 20% retention (near the top of the range reported), eq 1 gives $k = 3 \times 10^8$ for the racemization process. Cyclopropyl radicals and vinyl radicals undergo inversion and cis–trans isomerization, respectively, at measurable rates, but they are generally at least an order of magnitude faster than this. For these cases, at least, the D model may need some modification. Both Walborsky and Garst have suggested a possible participation of radical anions, $(RX)^{\bullet-}$. Electron transfer to simple alkyl halides either is dissociative or, at most, leads to extremely short lived intermediates. However, Walborsky's halides contain π electron systems, and such $(RX)^{\bullet-}$ species, e.g., with R aryl and benzyl, can have relatively long lives (the radical anion of 1-chloronaphthalene, for example, is reported[9] to have a rate constant for dissociation of 10^7 s^{-1}). To fit this into the D model, one might assume that when radical anions have any stability, they diffuse out into the solution before decomposing. If this is all that happens, the only effect would be to increase the average value of s in eq 1. However, if on recolliding with the Mg surface they can undergo further reduction and conversion to RMgX by a stereospecific process, Walborsky's results could be accounted for. As a matter of fact, the reduction of 1-bromo-1-methyl-2,2-diphenylcyclopropane by naphthalene radical anion occurs with some retention of stereochemistry in homogeneous solution[10] so a metal surface is not even required for a stereospecific step. Admittedly, it may be difficult to distinguish this formulation from one in which the radical anion sticks to the Mg surface until it reacts or decomposes, but Boche's results[10] seem to remove the need for invoking an adsorbed species with any special properties. Both formulations, incidentally, predict no retention of stereochemistry in the side products, and it would certainly be of interest to examine the application of the D model to halides *known* to have long-lived radical anions, e.g., containing naphthyl or other polynuclear aromatic groups. With or without elaboration, the difference between the two models is that the D model assumes that only the electron transfer processes occur at the Mg surface, while the A model proposes that all reactions occur there. Although the difference is subtle, it is more than semantic, since, in the D model, radicals are predicted to get, on the average, many molecular diameters out into the solution before reaction.

To me, the difficulty with the A model is that it depends upon the properties of putative absorbed radicals of appreciable life, which to date can be deduced solely from the data which one wishes to explain, so it is difficult to falsify. One cannot show that it is wrong, but it invokes several additional reactions of poorly characterized species and has little predictive power. The D model, in contrast, assumes the same properties of radicals (and perhaps also radical anions) as have been extensively studied in homogeneous solution and makes definite predictions based on reaction parameters which can be independently measured or estimated.

Since it is not clear how the A model can be tested, I believe that the best way of extending our knowledge is to continue to test the D model (suitably modified when required) by properly planned experiments. Any role of radical anions needs to be cleared up. Next, since product yields are very sensitive to δ, a particularly important point may be determining whether δ is indeed invariant or sensitive to the halide in RX, the state of the Mg surface, and the solution composition. Such experiments might be best done by allowing surface trapping to compete with some first-order process with a relatively large and well-established rate constant and keeping the rate of radical production low to minimize coupling reactions. Where the simple D model fails to match experiment, additional considerations such as radical anion participation will have to be added.

If the D model stands up, it can be used to clear up a number of other puzzles. Unless allyl Grignard reagents are prepared at high dilution or slow RX addition, they give relatively high yields of coupled products. Is this because of the known (allyl)X (allyl)MgX coupling reaction, or because the trapping of allyl radicals is relatively slow? Again, the Barbier reaction (a predecessor of the Grignard reaction in which RX and a substrate are reacted with Mg in a single step) sometimes gives quite different results from Grignard reactions. Is this because the carbonyl compound or other substrate is able to trap $R^{\bullet}$'s? Finally, as an example of the many loose ends which fill the literature, Sheldon Buckler, my first graduate student at Columbia, noted that bornylmagnesium chloride on carbonation gave acid with essentially complete retention of configuration, but on treatment with O_2 yielded a 56:44 mixture of bornyl and isobornyl hydroperoxides.[11] The results were puzzling at the time, but are now less mysterious. Autoxidation is a radical chain process, and the product distribution reflects a slight preference for addition of O_2 to the "bornyl" side of the free radical. The carbonation result, however, means either that the initial intermediate was predominantly trapped by a stereospecific process or that trapping, for some reason, occurred preferentially on the bornyl side. At the time, it was not obvious that the proper experiment was to repeat the carbonation with isobornyl chloride, and, as far as I know, this has never been done.

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