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COMMENTARY

Grignard Reagent Formation and Freely Diffusing Radical Intermediates

The Grignard reagent is one of the most useful, perhaps the most useful, of all synthetic intermediates.¹ Unfortunately, it is formed in a heterogeneous reaction occurring at a solid-liquid interface. No nonelectrochemical organic reaction occurring at a solid-liquid interface is understood at the mechanistic level that is typical for reactions in homogeneous solutions. An obvious reason for the shortfall is the lack of kinetic studies. For Grignard reagent formation, recent advances, using kinetics, promise to allow this gap to be filled.

Two classes of mechanisms of Grignard reagent formation are currently under active consideration, D ("diffusion") and A ("adsorption") models, which differ as to whether the intermediate radicals diffuse freely in solution or remain adsorbed at the magnesium surface. Figure 1 illustrates the basic D and A models.²⁻⁸ In a

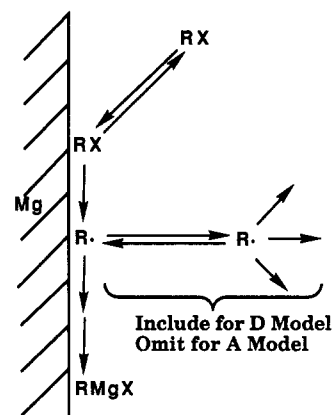


Figure 1. Basic D and A models. While in solution (D model), $R\cdot$ reacts with solvent, isomerizes, couples, etc.

(1) Kharasch, M. S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*; Prentice-Hall: New York, 1954.

(2) Garst, J. F.; Deutch, J. M.; Whitesides, G. M. *J. Am. Chem. Soc.* **1986**, *108*, 2490.

(3) Garst, J. F.; Swift, B. L.; Smith, D. W. *J. Am. Chem. Soc.* **1989**, *111*, 234.

(4) Garst, J. F.; Swift, B. L. *J. Am. Chem. Soc.* **1989**, *111*, 241.

(5) Garst, J. F., unpublished D-model calculations, 1988-1990.

(6) (a) Root, K. S.; Hill, C. L.; Lawrence, L. M.; Whitesides, G. M. *J. Am. Chem. Soc.* **1989**, *111*, 5405. (b) Lawrence, L. M.; Whitesides, G. M. *J. Am. Chem. Soc.* **1980**, *102*, 2493.

(7) Walborsky, H. M. *Acc. Chem. Res.* **1990**, *23*, 286.

(8) Walborsky, H. M.; Rachon, J. *J. Am. Chem. Soc.* **1989**, *111*, 1896.

(9) (a) Root, K. S.; Deutch, J.; Whitesides, G. M. *J. Am. Chem. Soc.* **1981**, *103*, 5475. (b) Rogers, H. R.; Deutch, J.; Whitesides, G. M. *J. Am. Chem. Soc.* **1980**, *102*, 226. (c) Rogers, H. R.; Hill, C. L.; Fujiwara, Y.; Rogers, R. J.; Mitchell, H. L.; Whitesides, G. M. *J. Am. Chem. Soc.* **1980**, *102*, 217.

(10) Garst, J. F.; Ungváry, F.; Batlaw, R.; Lawrence, K., submitted for publication.

(11) Bodewitz, H. W. H. J.; Blomberg, C.; Bickelhaupt, F. *Tetrahedron* **1975**, *31*, 1053.

(12) Some data were gathered and some determined by G. M. Whitesides and co-workers. Private communications, 1988-1990.

(13) Ashby, E. C.; Oswald, J. *J. Org. Chem.* **1988**, *53*, 6068.

(14) (a) Schaart, B. J.; Bodewitz, H. W. H. J.; Blomberg, C.; Bickelhaupt, F. *J. Am. Chem. Soc.* **1976**, *98*, 3712 and references cited therein. (b) Bodewitz, H. W. H. J.; Schaart, B. J.; Van der Niet, J. D.; Blomberg, C.; Bickelhaupt, F.; den Hollander, J. A. *Tetrahedron* **1978**, *34*, 2523.

(15) Molle, G.; Bauer, P.; Dubois, J.-E. *J. Org. Chem.* **1982**, *47*, 4120.

(16) Johnston, L. J.; Scaino, J. C.; Ingold, K. U. *J. Am. Chem. Soc.* **1984**, *106*, 4877.

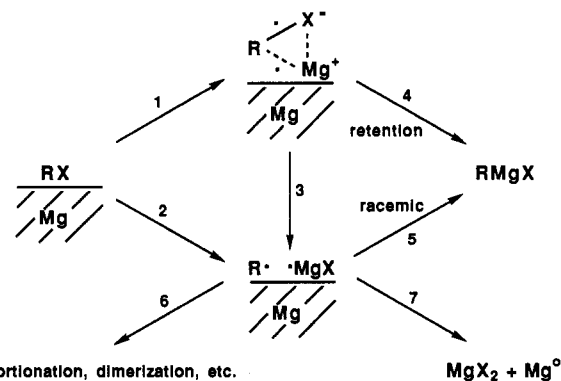


Figure 2. Elaborated version of the A model proposed by Walborsky and co-workers.

recent Account,⁷ Walborsky supports the mechanism of Figure 2, an A model in which the basic mechanism has been elaborated with additional hypotheses, tailored to certain experimental facts. My interpretations of the available data point instead to the basic D model for typical alkyl halides.

Tables I-IV summarize the present status as I see it.

Table I
Typical RX^{\bullet} ^a

fact	D model	A model
RMgX formation	○ ²⁻⁵	● ⁷
R [•] coupling and disproportionation	○ ²⁻⁵	●: reactions on surface ⁷
ratio of coupling to disproportionation same as for R [•] in solution ^{9a}	○: exact; R [•] are in solution	●: adsorption does not affect R [•] reactivities
little RH from R [•] + SH (0.5% maximum for hexyl bromide) ¹⁰	○ ^{4,10}	●: some R [•] desorb and react ⁷
radical isomerization ^{11,12}	○: many examples of isomerizations and other (pseudo-) first-order R [•] reactions competing with RMgX formation ^{2,4,12}	●: isomerization on surface ●: some R [•] desorb and isomerize
trapping by DCPH, TMPO ^{6,13}	○ ⁵	●: trapping on surface
less efficient trapping by DCPH than TMPO ^{6,13}	○ ⁵	●: under hypothesis that R [•] desorb and are then 100% trapped ^{7,8} ●: more efficient surface trapping by TMPO [•]
CIDNP [RR, RH, R(-H)] ¹⁴	●: potentially ○	●: reactions on surface
CIDNP in RMgBr ¹⁴	●: potentially ○	●: reactions on surface
different extents of isomerization in Grignard reagent (3%) and alkyl dimers (22%) for 5-hexenyl bromide ¹¹	○ ⁴	●: surface analogue of "cage" reaction and escape for [R [•] MgBr] ⁷
product quotient (RQ)/[(RR)(QQ)] ^{1/2} near 1 for 5-hexenyl bromide (R = 5-hexenyl, Q = cyclopentylmethyl) ^{11,13}	○ ⁴	●: surface [RX [•] Mg ⁺] pathway to RMgX ⁷ ●: predicts pathway 2 ⁴ ●: special reactivities of R [•] and Q [•] on surface
different reactions of Grignard and homogeneous-solution radicals ⁷	○: some explicit successes, no failures ^{4,10}	● ⁷

^a Especially RBr; e.g., R = hexyl, cyclopentyl, 5-hexenyl.

Table II
Atypical Halides^a

fact	D model	A model
partial retention of configuration ⁷	●: RX [•] intermediate ⁴	●: surface binding of R [•] ⁷ ●: RX [•] intermediate ⁷
no RH from R [•] + CH ₃ OD ^{7,8}	●: enhanced reactivity of R [•] at Mg surface ●: RX [•] plays enhanced role	● ●: same as D model
other aspects ⁷	similar to typical halides	similar to typical halides

^a E.g., 1-halo-1-methyl-2,2-diphenylcyclopropanes, 7-halobenzonorbornadienes, vinyl halides.

Table III
Cyclopropyl Bromide

fact	D model	A model
20–45% RH; at least 20% yield of RH from R [•] + SH, indicated by RS, SS, and S(-H) ¹⁰	○: calculation with same parameters as hexyl bromide except k_S (R [•] + SH) 10 ³ larger, consistent with literature ^{10,16}	●: under hypotheses of Walborsky and Rachon [σ R [•] (cyclopropyl) adsorbed more strongly than π R [•] ; R [•] that desorbs reacts with SH] ^{7,8}

Table IV
1-Bromoadamantane

fact	D model	A model
RR precipitate on Mg surface ¹⁵ without stirring: up to 60% RMgBr, with RH, RR, and solvent-derived products ¹⁵ with stirring: no RMgBr; RH, RR, and solvent-derived products only ¹⁵	●: RR is an expected byproduct; insoluble ○: D model with rate parameters adjusted for viscosity and reactivity of R [•] at surface ⁵ ●: stirring affects the nature and thickness of the precipitated layer, adversely affecting RMgBr formation ⁵	●: same as for D model ●: more desorption than usual ●: no effect of stirring (stirring does not affect layer next to surface, particularly when surface is coated with a viscous precipitate)

Under "fact" are experimental observations, and under "D model" and "A model" are predictions (deductions from the hypotheses). The symbol ○ denotes *quantitative* predictions (sometimes without parameter adjustment, sometimes with appropriate adjustment) that agree with the facts, ● denotes successful qualitative predictions, and ● denotes wrong predictions (inconsistent with the facts). The symbol ● denotes "accommodations", hypotheses supplementary to the basic D and A models that allow consistency with facts.

Comments. Unlike the D model, the A model and Figure 2 are incapable of quantitative predictions at present. Figure 2 comes close to being a nontheory, incapable of predictions and thereby nonfalsifiable. It is mostly a set of accommodative hypotheses.

Some of the A-model accommodations tabulated are

contradictory. Thus, accommodations state that adsorption both does and does not affect the relative reactivities of adsorbed radicals toward one another.

By erasing the magnesium surfaces from the intermediates in Figure 2, one can see clearly that adsorption of intermediate radicals is not required by observations of retention. The resulting mechanism predicts partial retention even when there is no surface.

Some of the arguments raised against the D model appear to be based on misconceptions about the intermediate radicals.⁷ In the D model, the radicals are not "in solution" in the same sense as radicals formed homogeneously. Instead, D-model radicals belong to surface-radical pairs, the behaviors of which are very different from those of both radical-radical pairs and individual radicals in solution.²⁻⁵ D-model Grignard radicals are calculated to have median

lifetimes near 10^{-7} s and steady-state concentrations approaching 10^{-3} M near the magnesium surface.²⁻⁴ Typically, alkyl radicals that do not suffer geminate reactions in homogeneous solutions have half-lives greater than 10^{-4} s and steady-state concentrations less than 10^{-6} M.⁵ These differences are sufficient to account for the observed differences in behaviors of Grignard and homogeneous-solution radicals. Adsorption is not required.

Summary. The basic D model promises to give better service and require less maintenance than the basic A model or Figure 2.

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