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About the Inhibition of Grignard Reagent Formation by *p*-Dinitrobenzene: Comparing the Mechanism of Grignard Reagent Formation and the $S_{RN}1$ Mechanism

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Both $S_{RN}1$-type reactions and Grignard reagent formation are inhibited by trace amounts (with respect to the halide) of *p*-dinitrobenzene (DNB) and other oxidising agents such as $CuCl_2$ or dioxygen. Both are believed to be triggered by an electron-transfer step. In this report we examine the patterns of reactivity shared by these two types of reaction. Although the two reactions display an amazing number of similarities, the chain character of the Grignard reaction mechanism has been rejected by major contributors to this field. We have performed new experiments to explore the inhibiting effect associated with the addition of trace amounts of *p*-dinitrobenzene during Grignard reagent formation. This inhibition involves very reactive nanoparticles of magnesium prepared by metal vapour synthesis. The magnesium slurries studied, in the absence of *p*-dinitrobenzene, display no induction period at all. If the *p*-dinitrobenzene is added to the solution containing magnesium slurries 25 min before adding the organic halide (here bromobenzene), the reaction is neatly inhibited but, if one waits long enough, the Grignard reagent is nevertheless formed. If, however, the same trace amounts of *p*-dinitrobenzene are diluted in the organic halide and this mixture is added to the magnesium slurries, the inhibiting effect is far less pronounced. The addition of the nBu$_4$NBr salt drastically diminishes the inhibiting power of DNB. These observations, in addition to the ESR study of radical anions formed in THF by the reaction of magnesium nanoparticles and DNB with various polyaromatics, suggest a mechanism for the observed inhibitions that involves a series of reversible adsorptions of the present species. This adsorption would depend on both thermodynamic and kinetic factors. Thermodynamics would favour the adsorption of DNB radical anions but C–X bond cleavage of the less strongly adsorbed aromatic radical anions would provide a kinetic driving force for displacing the equilibria in the direction of Grignard reagent formation. Salt effects could operate by displacing the equilibrium – adsorbed DNB radical anion or dianion versus solvated radical anion (with the counterion nBu$_4$N$^+$) – to the right, accelerating therefore the liberation of active sites on the magnesium surface. It appears that the inhibiting effect of the same compound finds its origin in two different molecular series of events in $S_{RN}1$ and in Grignard reagent formation. The heterogeneous character of the Grignard reagent makes it possible to envision the possibility of active sites even on nanoparticles, whereas the inhibition of the $S_{RN}1$ mechanism by DNB occurs in homogeneous solution.

Introduction

Grignard reagent formation pertains to a general class of reactions the synthetic utility of which goes against an old belief. This belief states that reactions involving the formation of radical species as the main route are likely to be of little use as synthetic tools: radicals are so reactive that the quantities of possible byproducts are thought to lower the yield of the targeted product. In this general class of reactions one also finds reactions involving persistent radicals,[1] radical-chain substitutions triggered by electron transfer ($S_{RN}1$)[2–5] or by a bimolecular homolytic substitution.[6,7] The recent two volumes edited by Renaud and Sibi emphasise some of the synthetic aspects emerging from this new trend.[8]

In this report we will concentrate on a comparison of the mechanistic aspects associated with the $S_{RN}1$ and Grignard reagent formation mechanisms. An important difference between the two mechanisms is that the latter is clearly heterogeneous. We examined in a previous contribution the consequences of this point.[9] Nevertheless, both classes of reactions are triggered by electron transfer to an alkyl or aryl halide; halide substrates, usually unreactive or poorly reactive, are involved in both reactions under mild conditions.

Substitution reactions induced by electron transfer to *p*-nitrobenzyl halides were discovered by Kornblum and coworkers in 1964.[10] Interestingly, the first report was only partly right. A new role devoted to a classical nucleophile was reported: the 2-nitropropane anion behaved both as a

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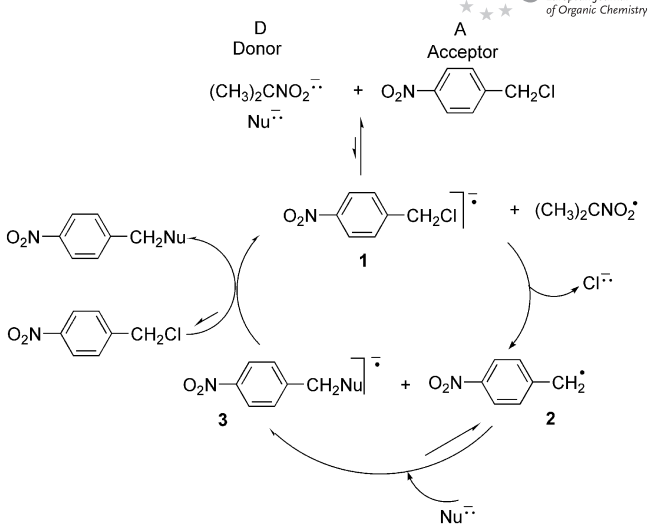
nucleophile and as a reducing agent. As a consequence, a *p*-nitrobenzyl halide radical anion was formed and its cleavage yielded a *p*-nitrobenzyl radical. This *p*-nitrobenzyl radical was supposed to couple with the radical formed by the oxidation of the 2-nitropropane anion to yield the final substitution product. This last proposition was abandoned two years later.[11,12] The actual fate of the *p*-nitrobenzyl radical was to add to the 2-nitropropane anion present in large excess; a radical anion was thus formed. This radical anion gave up an electron to another molecule of *p*-nitrobenzyl halide to simultaneously propagate a chain reaction and yield the observed substitution product (Scheme 1). Although in the original $S_{RN}1$ mechanism D was an anion, this mechanism was extended to also cover cases in which D was neutral. Another modification includes A, the radical anion of which has a vanishing lifetime (e.g., A = alkyl halides): the mechanism then bypasses the radical-anion step. The definite advantage of this proposition, made in 1966, was that it explained all the facts reported in 1964 plus the observation that trace amounts of *p*-dinitrobenzene, spin-trapping species or cupric chloride could inhibit the formation of substitution products. In fact, the rate constant for the coupling between *p*-nitrobenzyl and 2-nitro-2-propyl radicals is higher than the rate constant for the addition of *p*-nitrobenzyl radical to the 2-nitropropane anion. The overall competition, however, is dominated by the second type of interaction because the concentration of 2-nitropropane anions is far higher than that of 2-nitro-2-propyl radicals. This reaction mechanism was also later shown to apply to aromatic[3] and heteroaromatic substrates[13–15] and its generality then extended far beyond the narrow range of organic substrates.[5,16–18] Furthermore, under the general form displayed in Scheme 1, the mechanism also applies to other types of transformations such as the oxidative addition of organic halides to transition-metal complexes.[19–23] This point is relevant to this report because the formation of Grignard reagents may be viewed as an oxidative addition of organic halides to magnesium.



Scheme 1. Extending this scheme to the formation of a Grignard reagent, the role of donor would be played by the active sites of the magnesium metallic surface (see text).

As substitution reactions usually proceed by the more classical S_N1 or S_N2 mechanisms it was necessary to decide which diagnostic experimental observations could hint at the participation of such a mechanism whilst it was taking place. A series of experimental criteria were extracted from a large set of reactions belonging to the same class of reactions. These are detailed below in the order of decreasing importance.

1) Photostimulation: in contrast to classical S_N1 and S_N2 processes $S_{RN}1$-type reactions are usually strongly favoured by irradiation of the reaction mixture by a sunlamp (through pyrex).[24–29] Sonochemical activation has also been reported.[30]

2) Quenching of the reaction by trace amounts of oxidising agents (e.g., *p*-dinitrobenzene, $CuCl_2$) or radical traps (e.g., di-*tert*-butyl nitroxide).[26,31–34]

3) Entrainment of the reaction:[25,35–37] for example, the anion of $MeNO_2$ does not react with 1-iodoadamantane under irradiation, but excellent yields of 1-adamantylnitromethane are obtained in the photostimulated reaction in the presence of Me_2CO enolate ions.[38] A more quantitative view of entrainment connected with the chain character of the $S_{RN}1$ mechanism was provided by Scamehorn and Bunnett.[39] They studied the reaction of six substituted aryl iodides towards the pinacolone enolate anion in dimethyl sulfoxide in the dark. The reactivity was studied in two ways. In the first, they directly measured the reaction rates individually in experiments involving the substituted iodobenzenes. In the second, they measured the relative reactivity of each substituted iodobenzene versus bromobenzene in a competition experiment. The two approaches gave vastly different indications of the relative reactivity. The first approach indicated the *m*-methoxy-substituted iodide to be 400 times more reactive than the *p*-methyl-substituted iodide. In contrast, by the second method, the relative reactivity of the two compounds drops to two. In this second approach, the chain mechanism, a mechanism similar to entrainment, mixes the intermediates involved in the chain leading to the observed levelling effect.[39]

4) The presence of an induction period when the reaction is kinetically studied. Kinetic studies of $S_{RN}1$ reactions are rare. In the reactions of iodobenzenes with the pinacolone enolate anion, plots for the reactions of the *m*-methyl-, *p*-methoxy- and *p*-fluoro-substituted benzenes showed minor deviations early in the reaction, suggestive of an induction period. Such deviations were, however, absent for the three other iodobenzenes studied.[39]

5) In the electrochemical version of the reaction (the substitution is triggered by a cathode), catalytic quantities of electrons are sufficient to initiate the reaction.[40–43]

6) In the electrochemical version, some reactions demand the presence of mediators to provide good yields of the desired product.[44–47] This concept of electrochemical mediator was extended to thermal reactions by Rossi and coworkers.[48]

7) Detection of radicals by ESR, radical clocks, stereochemical-labelling or spin-trapping.[49,50]
8) The possible coexistence of radical and non-radical pathways starting from a unique electrophilic substrate–nucleophilic reagent couple.[2,5,43,51] This coexistence was also reported for the oxidative addition of alkyl or aryl halides to Ir^I, Pt^0 and Pd^0 complexes.[21,52,53] For both types of reactions, structural effects in the organic halide may lead to mechanisms no longer displaying the characteristics of radical intermediate involvement.
9) Striking and odd substituent effects: for example, the $S_{RN}1$ mechanism applied to the substitution of benzylic substrates demands the presence of nitro, cyano or CF_3 substituents on the aromatic ring to operate. This was understood by proposing that such substituents increased the oxidising power of the substrate leading, therefore, to an increase in the rate constant for the initiation step in the $S_{RN}1$ chain.[54] When the aromatic ring in these benzylic substrates has its oxidising power further increased by three nitro substituents, the substitution of the benzylic carbon by nucleophiles operates without any intervention of radical species. Meisenheimer complexes are first formed and the substitution of the benzylic carbon sometimes follows.[55,56] For the substitution of the haloaromatic substrates, the presence of a nitro substituent on the ring prevents the operation of the $S_{RN}1$ mechanism.[3]

In fact, in the great majority of reports proposing the participation of an $S_{RN}1$ mechanism, the first three criteria (and often only two of them) are supposed to be sufficient to establish the proposed mechanism in its chain version. The non-chain or very short chain version of the $S_{RN}1$ mechanism has been reported in some rare cases.[36,57–59] In one case the preliminary reports on the non-chain character were challenged.[60–62] Lund and co-workers designed a series of studies to demonstrate that a continuum of situations exists between the S_N2 and electron-transfer mechanism. In these studies, however, the chain versus linear electron-transfer mechanism was not specifically addressed.[63–65] It is interesting to consider which of these nine diagnostic criteria may be found in the reaction of magnesium with alkyl and aryl halides.

Test 1) Photostimulation has been reported only twice to improve the yield of Grignard reagent formation.[66,67] Under the form of sonochemical activation, it has been repeatedly used.[68–73]

Test 2) corresponds to experimental conditions often demanded for the successful preparation of Grignard reagents. It is well known that trace amounts of dioxygen, oxidising impurities or water can in some cases completely spoil such a preparation. These inhibiting effects associated with trace amounts of various chemicals have been studied quantitatively by several groups.[74–81] Noteworthy is the observation that radical-chain oxidative addition of organic halides to transition-metal complexes may be either accelerated or inhibited by given amounts of dioxygen.[21]

Test 3) corresponds to a very widely used method for making possible the preparation of Grignard reagents that would otherwise be difficult or impossible. The entrainment method was first reported to make easier the preparation of aryl Grignard reagents. The reluctant pentamethylphenyl bromide was mixed with ethyl bromide to make its reaction with magnesium possible.[82] This method was drastically improved when Pearson et al. proposed 1,2-dibromoethane as an entrainment agent.[83,84] Its mechanistic interpretation has given rise to various propositions, none of them, however, implying a chain reaction.[85,86]

Test 4) The preparation of Grignard reagents is well known to sometimes display annoying induction periods before its actually starts. This induction period has been quantitatively studied by several groups; some of them take this experimental observation as a strong hint of a chain mechanism.[74,76,78,81,87–93]

Test 5) The electrochemical induction, from metallic magnesium, of an organometallic preparation with the composition RMetalX is not known. It has, however, been reported for Hg. Peters and co-workers proposed a chain mechanism for this reaction because of the catalytic consumption of a few electrons necessary for it to occur.[94]

Test 6) Unless one considers that the naphthalene associated with magnesium in Bogdanovic's magnesium plays the role of a mediator, there are no clear cut examples of mediators used to improve the formation of Grignard reagents.[95–97] Nevertheless, for the formation of organolithium compounds from the appropriate alkyl halide, mediators have repeatedly been used.[98–101] Their actual role as mediator has recently been established by electrochemical studies.[102]

Test 7) The participation of radical intermediates in the preparation of Grignard reagents has been established beyond any doubt by spin-trapping, radical clocks, the nature of the byproducts formed and CIDNP. A good account of these studies may be found in reviews dealing with the mechanism of Grignard reagent formation.[103–105]

Test 8) The possible coexistence of radical and non-radical pathways is the most vexing mechanistic problem associated with the reaction producing the Grignard reagent. In the chronology of molecular events occurring between the initial reactants and the final products, where do these two routes cross? This problem was clearly raised 46 years ago in Walborsky and Young's report on the reaction between magnesium and optically active 1-bromo-1-methyl-2,2-diphenylcyclopropane.[106] The Grignard reagent obtained in this reaction had only partly retained the configuration of the carbon bearing the bromine in the substrate. Walborsky and Young showed, in the same report, that this loss of configuration occurred during the formation of RMgX and not after. Thus, RMgX was formed simultaneously by two competing routes. Since that time several explanations of this experimental observation (confirmed by several other studies using radical clocks) have been offered.[16,103,104,107–111] None of them has definitively proved its validity over the others. With respect to organic halides, the structural variations of which may lead to a reaction mechanism in which radicals seem to play no role, one can look at the formation of *anti*-7-benzonorbornadienyl Grignard reagents.[112]

Test 9) For substituent effects, again there is a striking similarity between Grignard reagent formation and the substitution chain reactions initiated by electron transfer. Indeed, Grignard reagents derived from aryl halides substituted by a nitro group have never been reported. In this case, only reduction of the nitro group seems to occur.[113] In contrast, aryl halides substituted by alkoxy groups (well known to decrease the electron affinity of these substrates) have repeatedly been reported as providing good yields of Grignard reagents.[114,115] Note, however, that the preparation of nitroaromatic Grignard reagents is feasible by halogen–magnesium exchange.[116]

Our first entry into the field of comparing the $S_{RN}1$ and Grignard reagent formation mechanisms was motivated by observations of metal-vapour-synthesised magnesium reacting with alkyl halides.[79,117] In these experiments, the magnesium (Mg*) is produced by in vacuo (6×10^{-4} mbar) vaporisation into a solution of THF maintained at –110 °C.[118,119] Determination of the size of magnesium clusters formed shows that we are dealing with nanoparticles.[120] The black suspension of magnesium clusters can then be transferred to a Schlenk tube where it can be kept under argon in the fridge for several months without any loss of reactivity. Their reactivity is remarkably high: such a black magnesium slurry has been reported to react, without an induction period, at –75 °C with cyclopropylmethyl bromide dissolved in THF. The Grignard reagent is formed in 2 hours.[121] With this type of magnesium we have also observed this very high reactivity and the absence of an induction period for alkyl and aryl halides. In a typical experiment, the reaction of 1-bromo-3-methylbutane with a four-fold excess of this active magnesium in THF provides after hydrolysis a quantitative yield of 3-methylbutane in less than 1 min at 20 °C and 90 min at –80 °C.[79] This high reactivity and the absence of an induction period are even more significant when one realises that, in these magnesium nanoparticle experiments, no initial MgX_2 is present. This salt has been shown to considerably lower the length of the induction time in the preparation of Grignard reagents.[85,86] In itself, this absence of an induction period and the high reactivity give credence to the propositions that the induction period, when present, corresponds to a cleaning of the metal surface, either from a passivating oxide layer or from traces of grease, allowing access to initially masked active sites.[104,122] Indeed, our method of magnesium preparation prevents the possibility of any parasitic oxidation of the metal or pollution by any other poisonous traces. Nevertheless, the reaction of 1-bromo-3-methylbutane with our active magnesium was strongly inhibited when we tried to perform it under argon or nitrogen (U quality) not specifically treated to remove the last traces of dioxygen. The study of other inhibitors previously reported in the literature confirmed this observation. Furthermore, DFT calculations suggest that alkyl radicals could add to magnesium clusters and the species formed should display higher reducing power than magnesium clusters themselves.[123] These species, which result from the addition of carbon-centred radicals to zero-valent magnesium, correspond to Mg^+ species. In Scheme 1 these intermediates are represented by the structure **3**. The alkyl groups bond quite strongly to the metal surface with bond energies in the range 25–40 kcal/mol.[124,125] Pulse radiolysis studies confirm the very high reducing power of Mg^+ species; thus, the electron transfer corresponding to the propagation step of the chain in Scheme 1 should be rapid.[126] This addition of radicals to the metal surface is also reminiscent of the early Kharasch and Reinmuth's suggestion: "surface adherent radicals, at least in part" should be involved in the formation of organomagnesium halides.[122] This series of facts, added to the previously discussed analogical features of the $S_{RN}1$ and Grignard reagent formation mechanisms, led us to propose an extension of the generalised Scheme 1 to the formation of Grignard reagents. Several authors have proposed chain mechanisms before but not in connection with the $S_{RN}1$ pathway.[88,89,127–129] A thorough discussion of the chain versus non-chain dilemma is presented in Van Klink's Ph. D. thesis.[105]

This proposition was controversial and has been discussed by several authors. Several arguments were advanced against it.

First, the reaction between 5-hexenyl bromide and magnesium in diethyl ether yields only small amounts of cyclised products (6%).[130,131] These small amounts contrast with the amount of cyclised products observed with such radical clocks when they are used in other homogeneous radical reactions.[132] Van Klink suggested that such small amounts discard the possibility of a chain mechanism leading to RMgX with one of the propagating species being a radical. Indeed, the rate constant of the radical cyclisation is in the range of 10^5 s^{-1} and therefore one should, according to this author, expect higher yields of cyclised products when the reaction is performed with 5-hexenyl halides.[105] This argument is not totally compelling: in Scheme 1, the step that competes with the intramolecular cyclisation involves a coupling between the nucleophiles (here Mg^0) and a radical. The rate constant of such a coupling reaction may reach values in the order of 2.5×10^9 M^{-1} s^{-1}.[50,133]

Secondly, Bickelhaupt and co-workers observed CIDNP effects in the formation of RMgX and the byproducts (RH and alkene) during the reaction of alkyl halides with magnesium (nothing was reported, however, for aryl halides). The appearance of such effects was demonstrated to be a result of the polarisation in radical pairs containing the two radicals R.[134–137] CIDNP effects have never been reported to occur in $S_{RN}1$-type reactions; we searched, without any success, for such effects in the reactions of *p*-nitrocumyl halides with the 2-nitropropane anion. The observation of CIDNP effects in radical-chain mechanisms is exceptional.[138] Thus, the CIDNP effects reported by Bickelhaupt and co-workers seem difficult to reconcile with a simple extended $S_{RN}1$-type mechanism. Nevertheless, Kramer and Osborn reported multiplet effects in the reaction of alkyl halide oxidative addition reactions with $[Pd(PEt_3)_3]$ and $[Pt(PEt_3)_3]$. Some of these reactions may possess chain character.[139,140]

Thirdly, Van Klink remarked that less than 0.05% of inhibitor with respect to the RX concentration may deceptively look like a very small amount. In fact, because only surface magnesium atoms are reactive, the inner ones being "hidden", the percentage of inhibitor with respect to magnesium is far higher than 0.05% even if the metal is in the form of nanoparticles.[105] This assessment is sensible and we will address it in this report.

Fourthly, Garst and Soriaga pointed out that under ordinary conditions, chain mechanisms can be ruled out because reaction rates are not drastically changed when significant amounts of radical intermediates are trapped with DCPH(D) or TEMPO.[103,141] This author also remarked that alkyl iodides and bromides (RX) can yield up to 50% RH and R–R. He proposed that such amounts resulting from the termination step seem too high for chains of appreciable length. This argument is not as compelling as the one based on the effect of radical traps because several authors[3,5] have reported $S_{RN}1$ reactions giving yields of products less than 60%.

To further study the role of inhibitors we concentrated on the effect of *p*-dinitrobenzene (DNB) on the reaction of bromobenzene (PhBr) with active magnesium. This aromatic halide was selected as an extension of our previous work with radical probes.[142] We describe the inhibitor effects with respect to the progress of Grignard reagent formation with time, ESR observations, salt effects and the role of the experimental methodology.

Results and Discussion

When a degassed THF solution of PhBr (0.052 M) was added within 0.5–1 min to a Schlenk tube containing a slurry of magnesium nanoparticles (3.4 equiv. with respect to PhBr) magnetically stirred in THF, the reaction was over in 50 min at room temperature (entry 1, Table 1). This experiment, performed in the total absence of dioxygen, shows that the slurries of metal-vapour-synthesised magnesium are highly reactive. This high reactivity is obtained without need of adding, at the start, triggering amounts of $MgBr_2$.[74] In entry 2 of Table 1, a degassed THF solution of DNB (0.03 mmol) was added to the magnesium nanoparticles in THF (2.63 mmol) and 25 min later a THF solution of PhBr (1.04 mmol) was added to this mixture. Under these conditions no Grignard reagent was formed after 1 h. However, after this time, the Grignard reagent began to slowly form (entry 3) and, after 4 days, the conversion was 100% (entry 4). Catalytic amounts of DNB (about 1% with respect to magnesium) increased the induction period.

The experiment in entry 5 was aimed at answering the question: what occurs if the inhibiting agent and PhBr compete for the clean surface of magnesium? When a degassed THF mixture of DNB (0.036 mmol) and PhBr (1.01 mmol) was added to magnesium nanoparticles (3.78 mmol), the reaction was over in 1 h (entry 5). The reaction proceeded as if no inhibitor was present in the reaction. Another way to prepare the Grignard reagent in the presence of catalytic amounts of *p*-dinitrobenzene uses salt effects. The data in entry 6 suggests that, under usual conditions, nBu$_4$NBr (0.03 equiv.) alone has no effect on the formation of the Grignard reagent. Then the reaction conditions corresponding to entry 2 in Table 1 were slightly modified: the THF solution of DNB was replaced by a THF mixture of DNB and nBu$_4$NBr (equimolar amounts). Under these conditions, the reaction again proceeded as if no inhibitor was present during the reaction (entry 7).

The induction period observed in the formation of Grignard reagents has received a variety of explanations. This induction period has been attributed to the autocatalytic or chain character of the mechanism.[88,89,92,93,143] Gzemski and Kilpatrick attributed the induction period to the time required for cleaning the magnesium surface.[87] The beneficial effect of sonication was attributed to the sonochemical desorption of inhibiting water or alcohol from the magnesium surface.[68] Studies of the beneficial effects of sonication on the formation of RZnX suggest that sonication may remove the surface oxide passivating layer.[144] Garst and Soriaga offered a similar explanation for the origin of the induction period in the formation of Grignard reagents.[104,145] Sonication may, however, have more complex

Table 1. Reaction of bromobenzene with Mg* under various conditions.

Exp.	[PhBr] [M]	Mg*[a] [equiv.]	DNB[a] [equiv.]	nBu$_4$NBr[a] [equiv.]	Time	Conversion[b] [%]	RMgBr[c] [%]
1	0.052	3.4	0	0	50 min	100	85
2[d]	0.037	2.5	0.03	0	1 h	[e]	0[e]
3[d]	0.037	2.5	0.03	0	18 h	87	67
4[d]	0.037	3.0	0.03	0	4 d	100	80
5[f]	0.040	3.7	0.036	0	1 h	100	[g]
6[h]	0.040	4.8	0	0.03	1 h	100	83
7[i]	0.036	3.5	0.03	0.03	1 h	100	72
8[j]	0.039	3.1	0.04	1	1 h	73	46

[a] Relative to PhBr. [b] Estimated from the remaining PhBr by GC with naphthalene as the internal standard. [c] Estimated by titration, see ref.[168]. [d] DNB was first added to Mg*. After 5–25 min of stirring, the halide was added. In entry 4, the purple complex with 1,10-phenanthroline did not appear on sampling after 50 min. [e] The purple complex with 1,10-phenanthroline did not appear but about 8% of C_6H_6 could be formed (GC). [f] DNB was added together with PhBr to the Mg* slurry. [g] The complex with 1,10-phenanthroline was observed but not titrated. The yield of benzene was about 89% (GC). [h] nBu$_4$NBr was added together with PhBr to the Mg* slurry. [i] nBu$_4$NBr was first added together with DNB to Mg*. After 25 min of stirring, the halide was added. [j] DNB was first added to Mg*. After 20 min of stirring, the halide was added together with nBu$_4$NBr.

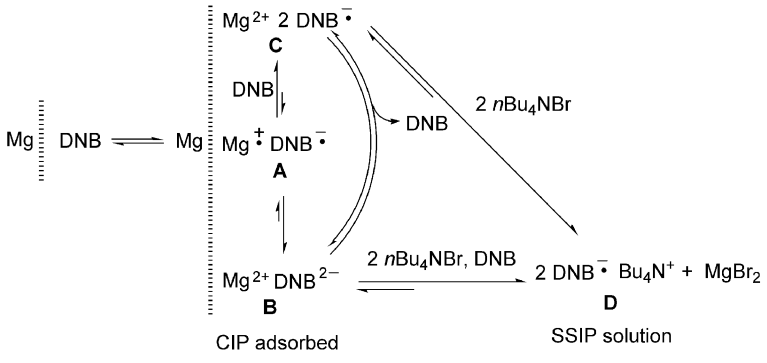
effects on the mechanism.[70] Maslennikov and co-workers proposed, within a Langmuir–Hinshelwood mechanism, a series of competitive adsorptions of the solvent, RX and the inhibitor on the magnesium surface.[90] Tuulmets and Heinoja explained the effect of a variety of inhibitors by postulating that they react with the Grignard reagent formed; as this reagent is supposed to clean the magnesium surface, this cleaning is prevented and an induction period results.[78,91] Garst et al. suggested that the induction period corresponds to the time needed to form $MgBr_2$, a recognised catalyst for the formation of Grignard reagents, in solution.[86]

We independently studied the reduction of several polynuclear hydrocarbons (ArH) with Mg*.[146] The first step involves a single electron transfer from Mg to ArH to form the CIP complex $ArH^{\bullet-}Mg^{\bullet+}$. The monovalent magnesium ($Mg^{\bullet+}$) is extremely short-lived and is thus elusive to its detection by ESR spectroscopy. The possible existence of such a species has been debated by several electrochemists but its identity still remains a puzzle.[147–150] Recent pulse radiolysis studies allowed the direct spectroscopic observation of such species. The authors suggested that such species have a reducing power so high that they would be better viewed as Mg^{2+}-solvated electron pairs.[126] The polynuclear hydrocarbons that we studied, from tetracene ($E_{1/2}$ = –1.34 V vs. NHE, dioxane/water) to pyrene ($E_{1/2}$ = –1.95 V vs. NHE, MeCN) yielded the corresponding radical-anion intermediates (ESR) and possibly the dianions.[151] The driving force for the dianion formation would be the high binding energy of Mg^{2+} with dianions compared with radical anions. The electronic configuration of Mg^0 being $(Ne)s^2$ and its strong electropositive character means that it tends the Mg^{2+} state.

Our observations on the patterns of inhibition in Grignard reagent formation suggested that a reversible adsorption of the DNB radical anion on the magnesium surface could provide a basis for the mechanism of inhibition (Scheme 2). DNB is a good electron acceptor ($E_{1/2}$ = –0.34 V vs. NHE, DMF).[152] It is easily reduced to the dianion **B** through the intermediacy of an adsorbed DNB radical anion, the counterion of which would be monovalent magnesium (**A**). Another possibility would be that $Mg^{\bullet+}$ attains the Mg^{2+} state reducing again DNB to give **C**, which could disproportionate to form **B**.[151] All these species are reversibly adsorbed on the surface of Mg as contact ion pairs (CIP) and thus the active sites of Mg remain occupied.[153,154]

So, whether the electron-acceptor molecule is DNB or ArH, the immediate reduction product is the CIP complex of the corresponding radical anion/dianion adsorbed on Mg. The role of an electrolyte such as nBu_4NBr is dramatic in that it drives the comproportionation equilibrium to the right-hand side favouring the growth of radical anions with nBu_4N^+ as counterions (**D**). Cation exchange with **C** could also give **D**. The species $DNB^{\bullet-}Bu_4N^+$ (or $ArH^{\bullet-}Bu_4N^+$) diffuse to the bulk of the solution as solvent-separated ion pairs (SSIP) and thereby fresh surfaces of Mg come into play until Mg is dissolved.

This explains our observations summarised in entries 2 and 8 of Table 1. The introduction of DNB 25 min prior to halide addition (entry 2) results in the occupation of Mg active centres by the $DNB^{\bullet-}/DNB^{2-}$ complex. With the progress of time (entries 3 and 4), the CIP diffuses away from the Mg surface in a slow process unless the salt is present which radically accelerates diffusion. Contrasting results were obtained under experimental conditions in which the halide is added along with the salt nBu_4NBr after the 20 min period of "DNB poisoning" (entry 8). In this case, 46% PhMgBr was formed as compared with 0% when the salt was absent (entry 2). Clearly the salt pulls the $DNB^{\bullet-}/DNB^{2-}$ CIP complex away from the Mg surface by a fast comproportionation process that favours the radical-anion route. Thus, the Mg surface is renewed and exposed to the competing molecules PhBr and DNB. In this competition, the organic halide is favoured over DNB because, even if its intrinsic oxidising power ($E°$) is lower, the equilibrated reaction is continuously irreversibly shifted towards the formation of alkyl or aryl radicals. In a situation in which PhBr is added to Mg along with DNB, the conversion is total (entry 5). This is the case in which the chemistry of the more reactive $Mg/Mg^{\bullet+}/PhBr^{\bullet-}$ CIP comes into play. The physical chemistry of the CIP versus SSIP species formed when metallic mirrors react with hydrocarbon acceptors has been thoroughly studied by Bock and Kochi and their co-



Scheme 2.

workers.[155,156] These studies involved alkali metal mirrors. For magnesium, a complicating factor is the formation of the highly reducing Mg^+ species after the first electron transfer from the metal.

In an attempt to mimic the above Mg/PhBr reaction, we selected an electron-acceptor hydrocarbon molecule such as perylene in place of PhBr in the presence of the salt. The radical anion of perylene is extremely stable and, expectedly, a blue-violet-coloured solution was formed that showed a high concentration of perylene radical anions, as characterised by ESR spectroscopy (Figure 1).[157] This is a simple case of Mg being consumed (dissolved) akin to alkali metal reduction.

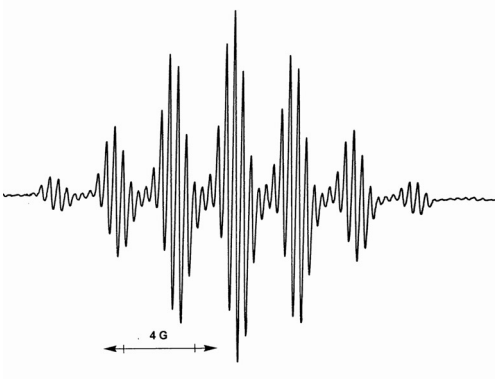


Figure 1. ESR spectrum of the perylene radical anion.

In another experiment, DNB (0.05 equiv.) was added to Mg (3.6 equiv.) 20 min prior to the addition of the perylene/salt mixture (1 equiv.). The reaction was marked by the appearance of a red colour. After 15 min, ESR spectroscopic examination of a sample showed the presence of DNB radical anions (Figure 2).[158,159] Subsequently, the solution began to assume a dark-blue colour. A sample withdrawn after 30 min from the reaction exhibited an ESR spectrum similar to that of perylene but was more complex apparently due to the background signals of $DNB^{\bullet-}$. These results suggest that DNB first acts at the Mg surface, clearly due to its low reduction potential relative to that of perylene. Then, however, a complex overall equilibrium is simultaneously formed between a donor and two different acceptors.

This set of experimental results suggests the following mechanisms for the inhibition caused by trace amounts of DNB. This mechanism has to be different for alkyl and aryl halides. Indeed, if the radical anions of a variety of aryl halides have been shown to display definite lifetimes, the radical-anion step is usually bypassed when an electron is transferred to an alkyl halide.[42] Such types of radical anions have been reported only at very low temperatures.[160,161]

Thus, the adsorption of the DNB radical anion on magnesium is reversible. When DNB is added before the addition of any organic halide, the equilibrium has time to fully form; most of the active sites present on the magnesium surface are neutralised. When the organic halide is

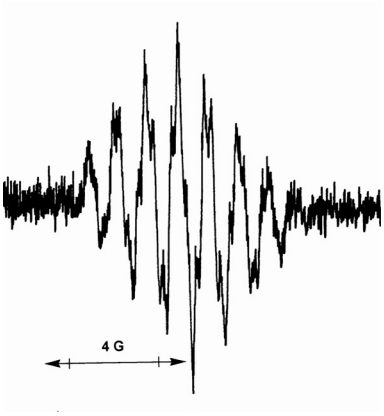


Figure 2. ESR spectrum of the DNB radical anion.

then added, its chances of undergoing electron transfer are drastically lowered; thus, the rate of RMgX formation is considerably lower. This holds both for alkyl and aryl halides. If the organic halide is added simultaneously with trace amounts of DNB, there is competition between the two types of reagents for the active sites present on the magnesium surface. The organic halide is favoured by its relative concentration and by the fact that the formation of the DNB radical anion is reversible, whereas for the organic halide, the reaction is driven by the irreversible consumption of the species formed by electron transfer. The role of added salt is reminiscent of what has been reported for solid–liquid phase-transfer catalysis.[162–164] Moreover, this salt effect should be connected to Knochel and co-workers' observations of the beneficial effect of LiCl in the insertion of magnesium into aromatic and heterocyclic bromides[165] and Rieke and Bales' report on the beneficial effect of KI addition in the preparation of Grignard reagents from active magnesium.[166]

Conclusions

The set of experiments described in this report suggest that inhibition by DNB is the consequence of an electron-transfer-mediated reaction at the surface of Mg. Cleaning of the Mg surface is facilitated by the salt, that is, $n\mathrm{Bu_4NBr}$, which pulls the cloud of ionic products away from the Mg surface. In the absence of the salt and under the usual conditions of Grignard reagent formation, DNB shows a marked inhibition when added to Mg prior to the halide. However, when DNB is added simultaneously with the halide, it no longer inhibits Grignard reagent formation. Here, the (more reactive) halide molecule successfully competes with the DNB molecule mainly because it irreversibly gives birth to very reactive species whereas DNB produces reversibly long-lived species. The addition of appropriate M^+X^- salts may prevent the inhibition by DNB by displacing the CIP equilibrium solid metal ion–anion radical towards SSIP species in which the radical anion is now in solution with the cationic part of the added salt and the metal surface is occupied by very reactive paramagnetic MgX species.

Experimental Section

General: THF was dried by heating at reflux and distilling from sodium under purified argon.[117] All manipulations were conducted under purified argon by standard Schlenk techniques. All glassware and transfer needles were oven-dried at 100 °C and cooled on a dual manifold vacuum/argon system just prior to use. THF solutions were degassed by at least three freeze–pump–thaw cycles. All reactions were performed at room temperature and with magnetic stirring. The preparation and manipulation of the Mg/THF slurry (Mg*) have been described previously.[117] Gas chromatographic analysis was performed with a Fisons GC 8000 chromatograph using a BPX5 capillary column (SGE, 25 m × 0.22 i.d.) with helium as the carrier gas and a flame ionisation detector. The following temperature program was used: injector: 280 °C; detector: 250 °C; 50 (10 min) to 280 °C (5 min) at 5 °C min^{-1}. Peak area integrations were performed by electronic integrations with a Spectra Physic Integrator. Naphthalene was used as an internal standard and all analytical results were corrected by the calculation of flame ionisation detector relative response factors using the effective carbon number concept.[167] Electron spin resonance (ESR) spectra were recorded with a Varian E9 spectrometer. The yields of the Grignard reagents were estimated by the method of Watson and Eastham.[168]

Reaction of Bromobenzene with Mg*: A solution of bromobenzene (0.165 g, 1.05 mmol) in THF (20 mL) was added within 0.5–1 min to a Schlenk tube containing Mg* (0.086 g, 3.54 mmol). After stirring for 50 min, the reaction mixture was transferred to another Schlenk tube equipped with a transfer needle connected to a small cylinder tied to a paper filter. Then the solution was filtered under a slight positive pressure of purified argon into a flask containing 1,10-phenanthroline (1–2 mg). A purple coloration appeared immediately. Titration to the colourless end-point, usually with 1-BuOH in xylene, gave the yield of the Grignard reagents. The reaction mixture was washed with aqueous NH_4Cl solution and brine and then dried ($MgSO_4$). The organic layer was analysed by gas chromatography.

The reaction yielded benzene. No dimer (biphenyl) was formed. The conversion was estimated from the remaining bromobenzene. Filtration, to remove Mg* excess, led to some mechanical loss. The yield of Grignard reagent was probably underestimated relative to the conversion.

Inhibition with 1,4-Dinitrobenzene: In a Schlenk tube, 1,4-dinitrobenzene (0.084 g, 0.5 mmol) was dissolved in THF (50 mL). This solution was then degassed and stored under argon.

The THF solution (3 mL) of 1,4-dinitrobenzene (0.01 M, 0.03 mmol) was added to a Schlenk tube containing Mg* (0.064 g, 2.63 mmol). After stirring for 25 min, a solution of bromobenzene (0.163 g, 1.04 mmol) in THF (25 mL) was added within 2 min. After 1 h, an aliquot of approximately 10 mL was transferred to another Schlenk tube, filtered, titrated and worked up as described previously. After 18 h, another sample was studied. This experiment was duplicated and samples were removed for analysis after 50 min and 4 d (Mg* and DNB were stirred 5 min before the addition of PhBr).

A solution of 1,4-dinitrobenzene (6 mg, 0.036 mmol) and bromobenzene (0.159 g, 1.01 mmol) in THF (25 mL) was added to a Schlenk tube containing Mg* (0.092 g, 3.78 mmol) within 1 min. After stirring for 1 h, the reaction mixture was transferred to another Schlenk tube, filtered into a flask containing 1,10-phenanthroline and then quenched with 1-BuOH in xylene. After work-up, the organic layer was analysed by gas chromatography.

Inhibition in the Presence of nBu$_4$NBr: A solution of bromobenzene (0.156 g, 1.00 mmol) and nBu$_4$NBr (0.011 g, 0.034 mmol) in THF (25 mL) was added to a Schlenk tube containing Mg* (0.117 g, 4.81 mmol) within 1 min. After 1 h, titration and work-up were performed as described above.

A THF solution (3 mL) of 1,4-dinitrobenzene and nBu$_4$NBr (0.03 mmol of each) was added to a Schlenk tube containing Mg* (0.086 g, 3.54 mmol). After stirring for 25 min, a solution of bromobenzene (0.157 g, 1.00 mmol) in THF (25 mL) was added. After 1 h, titration and work-up were performed as described above.

A THF solution (2.5 mL) of 1,4-dinitrobenzene (0.016 M, 0.04 mmol) was added to a Schlenk tube containing Mg* (0.079 g, 3.25 mmol). After stirring for 20 min, a solution of bromobenzene (0.166 g, 1.06 mmol) and nBu$_4$NBr (0.330 g, 1.02 mmol) in THF (25 mL) was added within 2 min. After 1 h, titration and work-up were performed as described above.

Reductions of Perylene: A THF solution (4 mL) of 1,4-dinitrobenzene (0.01 M, 0.04 mmol) was added to a Schlenk tube containing Mg* (0.065 g, 2.67 mmol). After stirring for 20 min, a solution of perylene (0.189 g, 0.75 mmol) and nBu$_4$NBr (0.241 g, 0.75 mmol) in THF (25 mL) was added within 1 min. After 5–10 min, the yellow colour became red. After 10–15 min, an aliquot was transferred to an ESR tube and the radical anion of 1,4-dinitrobenzene was identified by ESR spectroscopy. After 15–20 min a blue colour appeared. After 30 min, an aliquot was transferred to an ESR tube and the radical anion of perylene was identified by ESR spectroscopy. The sample was later diluted with degassed THF to increase the resolution.

Independently, the ESR spectra of the radical anions of 1,4-dinitrobenzene and perylene[157] were recorded after reaction with Mg*/nBu$_4$NBr. From the spectrum of the radical anion of 1,4-dinitrobenzene it appears that the two nitrogen atoms are not equivalent in their coupling behaviour, in line with observations reported earlier. A similar spectrum was reported in the reduction of DNB by sodium or magnesium in the presence of 1,2-dibromoethane.[158,159]

Note Added in Proof (March 18, 2010): In this text (Test 9) we wrote that Grignard reagents directly derived from aryl halides substituted by a nitro group were never reported. A recent reference[169] seems to use such Grignard reagents obtained from Rieke's magnesium.

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