

Alkyl halides reactions with cathodes or with magnesium. Grignard reagent studied with radical clocks. What is the step competing with the isomerisation of the intermediate radical?[†]

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Received 15 November 2005; revised 13 January 2006; accepted 19 January 2006

ABSTRACT: In the mechanism of reaction of Grignard reagent formation for alkyl halides (RX), it is generally assumed that the alkyl radical, formed by the electron transfer from the metal to this halide, reacts rapidly with the paramagnetic MgX^\bullet species. The previous comparisons of aryl halides reactivity toward magnesium and their reactivity toward a cathode strongly suggested that MgX^\bullet species are not, for the aryl halides, compulsory to rationalise the observed facts. The aryl radicals formed by electron transfer from the metal to the aryl halide would undergo a rapid second electron transfer to yield carbanions transformed into $RMgX$ by reaction with MgX_2 . In contrast, for the alkyl halides, the reduction of the rapidly formed alkyl radicals into carbanions has seldom been discussed as a possible fate for these radicals, the main discussed fates being dimerisation, disproportionation, hydrogen abstraction from the solvent, rearrangement or coupling with MgX^\bullet radicals. Two main differences distinguish the reactivity of alkyl halides from their aryl halides counterpart. First, the radical anions of aryl halides may have a given lifetime whereas electron transfer to alkyl halides is concerted with the cleavage of the molecule. Second, the aryl radicals display far stronger oxidising properties than the alkyl radicals. The counterpart of this property is that aryl carbanions display weaker reducing properties than the alkyl ones. In this report, putting in perspective Grignard reaction and the experimental results obtained with identical radical clocks in electrochemistry, we tentatively provide an answer to the question raised in the title. The comparison of electrochemical patterns of reactivity of selected alkyl halides and the evolutions of yields in the preparation of Grignard reagent suggest a new explanation for the lower yields generally observed when alkyl iodides are the starting substrates. It involves an autocatalytic reaction where carbanionic species formed from the alkyl radicals and diffusing away from the metal surface, transfer one electron to the alkyl halide; the result would be the creation of two radicals leading to an increased amount of by-products. If the carbanionic mechanism were to be retained for the formation of alkyl Grignard reagent one would have to admit that the magnesium surface behaves as a cathode displaying high current densities reminiscent of microelectrodes. Copyright © 2006 John Wiley & Sons, Ltd.

KEYWORDS: electron transfer; radical clocks; Grignard reagent formation; carbanions; RX cathodic reactions; microelectrodes; leaving group effects; autocatalysis

INTRODUCTION

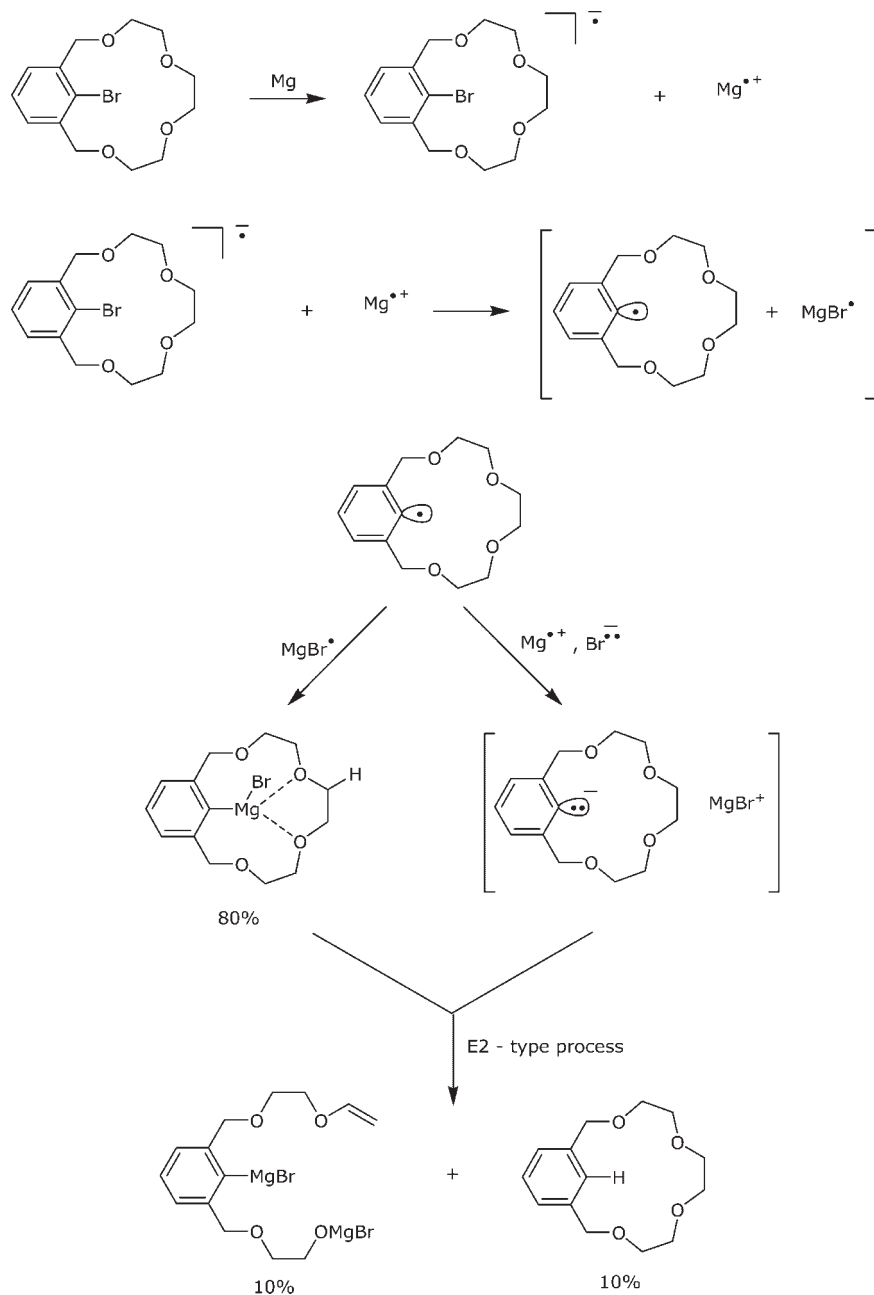
In 1988, Bickelhaupt's group provided the first experimental evidence of the involvement of carbanionic species in the formation of aryl halide Grignard reagents.¹ This first observation was made possible by the very special structure of the studied aryl halide: 2-bromo-1,3-

xylylene-15-crown-4. The formation, besides the normal Grignard reagent (80%), of two by-products (10% each): a protonated product and a ring opened one could be rationalised by the mechanism shown in Scheme 1. In this mechanism, the ether cleavage occurs because of an activation of the ethylene group by coordination of the neighbouring oxygens with magnesium. Thus, the already formed Grignard reagent would be attacked intermolecularly by an intermediate carbanion formed in the pathway leading to the Grignard reagent. This intermediate carbanion would be formed by a rapid reduction of the aryl radical created by the cleavage of the aryl halide radical anion. This first observation was further confirmed by a series of experiments.^{2,3} An excellent account of

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[†]This article is published as part of the special issue *Festschrift for Norma Nudelman*.



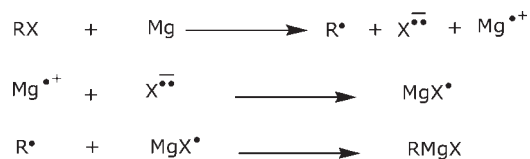
these studies and also a comprehensive critical review of the various mechanisms proposed for the formation of Grignard reagents is given in van Klink thesis.⁴ The intervention of carbanions in aryl halides Grignard reagent formation was then independently proposed by two groups.⁵⁻⁸

In Scheme 1, the fate of the aryl radical is ruled by the competition: coupling with the radical species MgBr^\bullet (or for rapid radical clocks, cyclisation)⁵ versus reduction by a second electron transfer (ET) either from the metal surface, from $\text{Mg}^{\bullet+}$ or from MgBr^\bullet .³

Garst's proposal for a dianion intervention would, in this scheme, bypass the aryl radical intermediate because the originally formed radical anion would accept a second

electron and the formed dianion would rapidly cleave to give the aryl carbanion and a bromide anion.⁶

In the mechanism that we propose as an extension of the electrochemical model of kinetic zones, a slightly different mechanism could occur.⁹ The radical anion formed by the first ET could, at least in part, diffuse toward the bulk of the solution. It would give birth, by its cleavage, to an aryl radical and a halide anion at a given distance of the metal surface. On its way back to the metal surface, the aryl radical could be reduced by the radical anions present in the vicinity of this surface or at the metal surface itself. In the vicinity of the surface one would therefore have the species radical anion, magnesium dibromide (corrosion approach of the Grignard


Scheme 2

reagent),¹⁰ formed Grignard reagents (from the reaction between carbanions and MgBr_2) and aryl carbanions having not yet reacted with MgBr_2 . These carbanions could react with the already formed Grignard reagents to yield the two by-products described in Scheme 1. If this slight modification holds, one would expect that the addition of MgBr_2 in Bickelhaupt's mixture from the start would decrease the percentage of by-products in a way reminiscent of Garst's observation for aryl radical clocks.⁶ In this proposition, the intervention of MgBr^\bullet radicals is not needed.

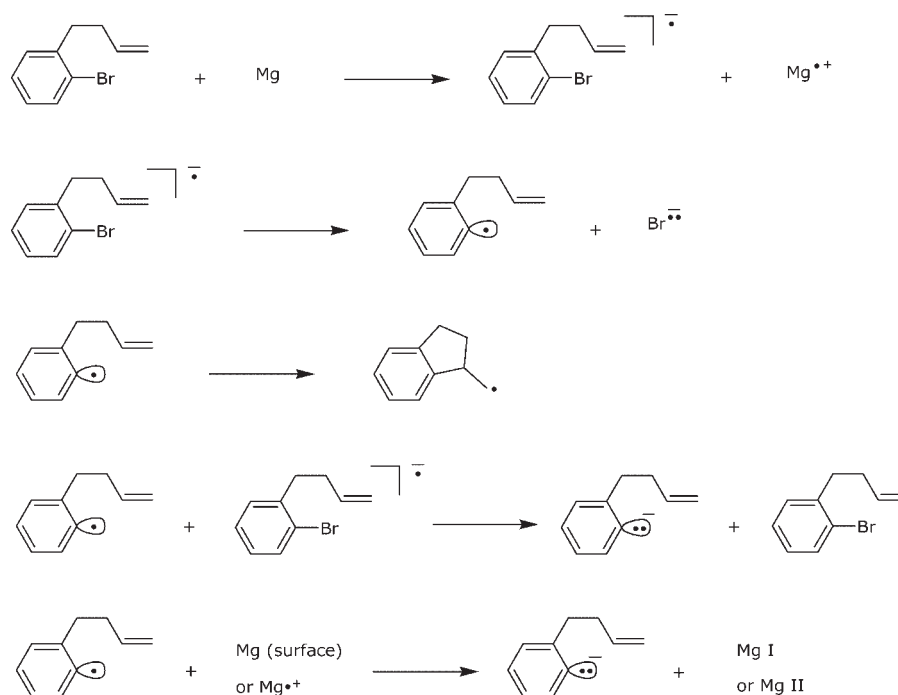
The currently adopted mechanism for alkyl halides Grignard reagent formation involves the intervention of MgX^\bullet radicals as central species (Scheme 2).^{4,11-19}

In this mechanism, the fate of the alkyl radical is ruled by a competition between a set of classical elementary steps for an alkyl radical (formation of radical pairs, dimerisation, disproportionation, and atom transfer) and a coupling of the radical with MgX^\bullet which forms the Grignard reagent.²⁰ There is no carbanion intermediate on the route going from alkyl halides to the Grignard reagent. However, in his review summarising more than 30 years of experiments and thoughts about the mechanisms of ET

and the Grignard reagent, Garst critically examines the arguments on which the participation of MgX^\bullet are based and prefers the hypothesis in which the route going from the alkyl radical to RMgX goes through a carbanion.⁷

In another publication,⁹ we propose to apply the model built by Savéant's group to account for the selectivity observed when an aryl halide is reduced at a cathode.²¹⁻²⁶ This model considers that, for these compounds, the selectivity is settled in a zone where gradients of concentrations for substrates, intermediates and products in the vicinity of the solid surface rule the macroscopic selectivity. It, therefore, involves kinetics where the concentrations of compounds have to be derived with respect to time but also with respect to the distance to the solid surface. When aryl halide radical clocks are considered in the context of Grignard reagent formation, Scheme 3 shows that the main step competing with the radical cyclisation is a rapid reduction of the aryl radical by the Mg surface on one side but also by the radical anion of the starting radical clock. This competition differs from that shown in Scheme 2. The relative participation of the Mg surface and radical anions in the reduction step critically depends on the lifetime of aryl halide radical anion but also on other factors (kinetic zone approach).

The differences between the electrochemical model and the diffusion model (D) proposed by Garst, is clearly illustrated when one returns to Ashby's in depth study of the reaction of various alkyl centred radical clocks towards magnesium.¹⁶ The similarity is that both models propose that the radicals diffuse towards the solution and, part only of them returns to the metallic surface to yield the Grignard reagent. This interpretation contrasts with


Scheme 3

the Kharasch–Walborsky model where the radicals are supposed to remain adsorbed on the metallic surface.^{17,18,27} The main consequence is the introduction of gradients of concentrations for the reactive species in both D and electrochemical models. However, in the D model, as applied by Ashby, when the radical returns to the metallic surface it reacts specifically with an MgX^\bullet present on the metallic surface, whereas, in the electrochemical model it is reduced by any metallic atom of the surface. Furthermore, in the D model, the radical returning to the metallic surface is supposed to do no ET chemistry on its travel back to the surface, whereas the electrochemical model supposes (at least for some aromatic halides) that, on its way back, the radical may be reduced into carbanion by the radical anions present in the close vicinity of the metallic surface.

The purpose of the present report is to examine if the mechanism of Grignard reagent formation is intrinsically different for alkyl halides and aryl halides. And, more specifically, if carbanionic species are involved in the route toward the Grignard reagent for both substrates.

ELECTROCHEMICAL STUDIES OF ALKYL CENTRED RADICAL CLOCKS

The starting point for the extension of the kinetic zone model to the selectivity observed in the reactions between aryl halides and magnesium was the comparison of electrochemical results with the reaction of aryl centred radical clocks toward magnesium.²⁸ We will adopt the same methodology: compare the pattern of reactivity of alkyl centred radical clocks towards a cathode and towards magnesium. Some electrochemical experiments on radical clocks will also be described because of their conceptual importance even if their reactions with magnesium have not yet been reported.

General electrochemical properties of alkyl halides

The cyclic voltammograms (0.1 V s^{-1}) of primary, secondary and tertiary butyl iodides and bromides (concentration 2 mM) on a glassy carbon electrode in $\text{DMF} + 0.1 \text{ M NBu}_4\text{BF}_4$ at 10°C make it possible to compare the ease of reduction of the radicals formed from alkyl halides with the ease of reduction of the starting halide.²⁹ For most aryl halides, the aryl radicals formed by the cleavage of the corresponding radical anion were easier to reduce than the starting aryl halide.²² The situation is more complex for alkyl halides. The six studied alkyl halides part into three groups. The first group contains *n*-BuBr, *sec*-BuBr, and *n*-BuI whose voltammograms display a single two-electron wave, respectively, at -2.61 V , -2.39 V , -2.09 V (vs. NHE). This corresponds to a situation where the R^\bullet radicals

formed by the one-electron reductive cleavage of the C—X bond are reduced at a potential which is positive or, at least, equal to the potential at which the reductive cleavage occurs. The second group contains *sec*-BuI and *tert*-BuI whose voltammograms display two one-electron waves, respectively at -1.81 and -1.67 V for the wave corresponding to the reductive cleavage. The second wave, which appears at more negative potentials (-2.26 and -2.4 V vs. NHE for *sec*-BuI and *tert*-BuI, respectively), indicates that the R^\bullet radicals formed in these cases are more difficult to reduce than the starting alkyl halide. An intermediate situation holds for *t*-BuBr: a single two-electron wave appears at -2.27 V ; its shape suggests, however, that the reduction of the R^\bullet radical is only slightly negative to that of RX. The ease of reductive cleavage decreases in the order RI, RBr, RCl and in the order tertiary, secondary, primary for the nature of the R group. The ease of reduction of the R^\bullet radical decreases in the order *n*, *sec*, *tert*.

The alkyl chlorides could not be examined by these authors because of the very negative potential demanded to effect the reductive cleavage.^{29,30} By extrapolation of the observed trends for alkyl iodides and alkyl bromides one expects that, for alkyl chlorides, the R^\bullet radicals formed by the one-electron reductive cleavage of the C—Cl bond will be reduced at a potential which is positive to the potential at which the reductive cleavage occurs. Those alkyl halides for which such a situation holds should exhibit a single two-electron reduction wave leading predominantly to the R^- carbanion because the reduction of R^\bullet radical is easier than that of the starting alkyl halide. The situation is, apparently, similar to the one met with aryl halides.²² Actually, there are two differences counteracting each other. The first difference is that most aryl halides form radical anions upon ET while reduction of alkyl halides does not generally lead to the formation of radical anion but to concerted C—X bond cleavage. As a consequence, the radical anions of aryl halides have a higher probability to diffuse away from the cathode surface. Those radical anions, which will have diffused away, will give birth to aryl radicals having good chances to develop, in solution, a radical rather than carbanion chemistry. The first difference would then favour a radical chemistry for the aryl substrates with respect to the alkyl ones. The second difference is that aryl radicals are far better oxidising agents than alkyl radicals.^{31–37} Indeed, phenyl radical is about 1 V easier to reduce than alkyl ones. Aryl radicals should, from this point of view, display a more carbanionic chemistry.

Those alkyl halides for which the reduction of the R^\bullet radical is more difficult than that of the starting halide would give birth to radicals having more chance to display others facets of the radical reactivity (dimerisation, disproportionation, atom transfer) than only one-electron reduction. One expects reactivity with higher radical character for this class of substrates. Secondary

and tertiary iodides, tertiary bromides should be in this class. We will see (Schmit's paragraph), another reason why such a radical chemistry could be favoured for these types of halides.

The reduction at glassy-carbon electrodes of the series CF_3Br , CF_3I , $\text{C}_6\text{F}_{13}\text{I}$ and $\text{C}_8\text{F}_{17}\text{I}$ in aprotic solvents containing tetralkylammonium salts illustrates also the radical *versus* carbanionic dichotomy of reactivity depending upon the relative ease of reduction of the created radicals with respect to the starting substrate.³⁸ For this series, Savéant's group found that $\text{R}_\text{F}^\bullet$ radicals are easier to reduce than alkyl radicals on thermodynamical grounds. As alkyl radicals, however, they display a high intrinsic barrier to reduction. More specifically, the radical *versus* carbanionic chemistries of CF_3Br and CF_3I depend on the competition between the rate of ET from the cathode to CF_3^\bullet radicals and the rates of other reactions that these radicals may undergo in the solution (here, mainly H-atom transfer from the solvent). The rate of ET may be modified as required by changing the potential of the cathode. In the potential region -1.46 V to -1.56 V vs. NHE, a balanced competition between the radical chemistry (H-atom transfer) and reduction of the CF_3^\bullet radicals is settled. Hence, the cyclic voltammograms of CF_3Br show a two-electron wave at the peak potential (-1.81 V vs. NHE) whereas CF_3I one exhibits two waves. The first one (one-electron wave) appears at -1.28 V and corresponds to the easier uptake of one electron by the iodo substrate. The second reduction wave appears in the region of -1.56 V and corresponds to the reduction of CF_3^\bullet radical into a carbanion. These results let expect that the reduction of CF_3I at an inert electrode gives rise to CF_3^\bullet radical chemistry. For CF_3Br , the direct cathodic reduction at the foot of reduction wave gives rise to mixed carbanionic-radical chemistry. To increase the weight of the radical component, one would have to effect the reduction using a mediator having a standard potential positive to -1.46 V vs. NHE.

One may recall, at this point, that Ashby's group could obtain alkylmagnesium fluorides by reaction of alkyl fluorides with magnesium in THF or 1,2-dimethoxyethane only when catalysts such as iodine or 1,2-dibromoethane were added to the medium. Under the most favourable conditions $\text{C}_6\text{H}_5\text{F}$ and PhCH_2F failed to react with magnesium.^{39,40} Rieke, however, was able to prepare the Grignard reagent of *p*- $\text{FC}_6\text{H}_4\text{Me}$ in 70% yield by refluxing this fluoride with anhydrous MgCl_2 , potassium and potassium iodide in THF for 1 h.⁴¹

Peters's studies of electrochemical cyclisations. Leaving group effects, acidic additives and electrode potential effects on radical clocks selectivity

In dimethylformamide containing tetramethylammonium perchlorate, Peters's group performed the preparative-

scale electrolyses and recorded the cyclic voltammograms for reduction of 1-iodo-5-decyne and 1-bromo-5-decyne at vitreous carbon cathodes.⁴²

At scan rate of 100 mV s^{-1} the peak potentials for reduction of 2.5 mM solutions of 1-iodo-5-decyne and 1-bromo-5-decyne were, respectively, -1.93 V and -2.41 V vs. NHE. These values, very close to those measured under the same conditions, for 1-iododecane and 1-bromodecane strongly suggest that the voltammetric waves for the two acetylenic halides correspond to overall two-electron reduction of the carbon-halogen sites.

Controlled potential electrolyses of both halides yielded pentylidenecyclopentane, 5-decyne, 1-decen-5-yne, 5-decyn-1-ol, and, possibly, small amounts of telomeric species (Scheme 4). Pentylidenecyclopentane was shown to result from the cyclisation of the 5-decyn-1-yl radical formed by the dissociative ET to the substrate. The cyclised radical would then abstract hydrogen from dimethylformamide. The alternative pathway: reduction of the cyclised radical followed by protonation of the formed carbanion was shown to be of minor importance (about 10%). 5-decyne occurred by protonation of the carbanion generated upon one-electron reduction of the 5-decyn-1-yl radical. This protonation was mainly affected by the tetramethylammonium cation. Residual water in the solvent was responsible for the presence of 1-decen-5-yne. This water would be transformed into the hydroxide anion; in the aprotic polar medium this base rapidly deshydrohalogenates the starting substrate to give the observed 1-decen-5-yne. If this base effects a substitution on the starting material rather than elimination, then, 5-decyn-1-ol is obtained. This overall mechanistic representation is shown in Scheme 4.

This general scheme undergoes modifications depending upon the structure of the starting substrate, its concentration and the presence of certain additives.

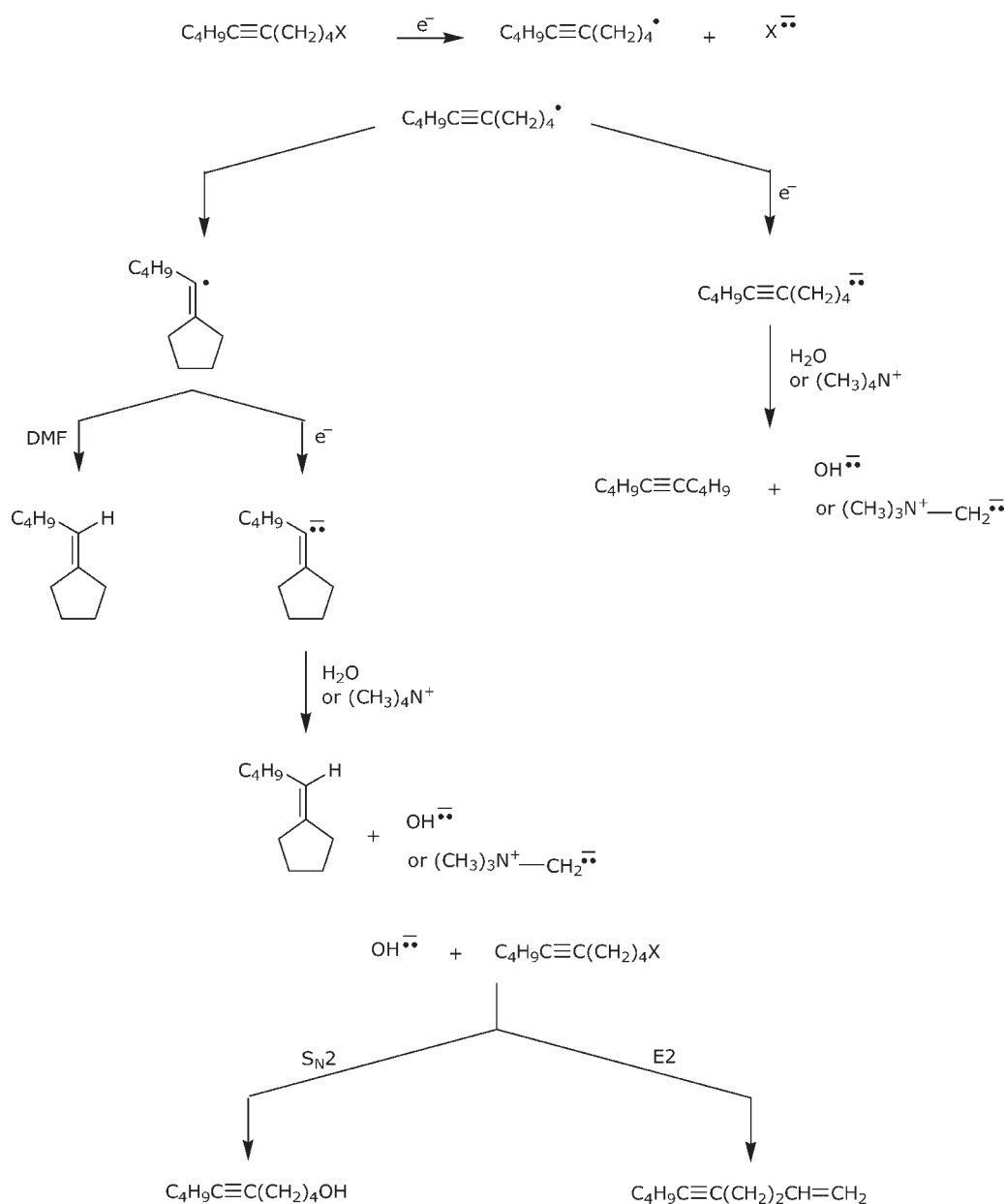
Much more pentylidenecyclopentane is formed when 2.5 mM solutions of 1-iodo-5-decyne (46% yield) are electrolysed than when the starting substrate is 1-bromo-5-decyne (5% yield). The opposite trend holds when one looks at percentages of 5-decyne: 11% for the iodo substrate *versus* 41% for the bromo one. These evolutions may be understood if one recalls that the electrolysis of the iodo derivative is effected at a potential of -1.86 V whereas the one of the bromo one demands a potential of -2.36 V (vs. NHE). Therefore, the 5-decyn-1-yl radical formed for both substrates was born in a more reducing medium for the bromo substrate than for the iodo one. This interpretation is substantiated by the observation that when the potential of the carbon electrode is made more negative for the electrolysis of the iodo substrate the yield of pentylidenecyclopentane declines as the quantities of 5-decyne and 1-decen-5-yne increase.

When the concentrations of 1-iodo-5-decyne were changed from 1 to 10 mM in a dimethylformamide solution containing 0.1 M of tetramethylammonium perchlorate in electrolysis experiments performed at

–2.21 V, the percentage of cyclised product was double of the one observed at the 1 mM concentration. The percentages of 5-decyne, 1-decen-5-yne and 5-decyn-1-ol, all decreased. Two new products appeared. About 10% of 1-iododecadiene was formed, probably via a base catalysed isomerisation. Small amounts of 5,15-eicosadiyne (1–2%) were also identified: increase in the concentration of the starting substrate seems to favour the reaction of dimerisation of the 5-decyn-1-yl radical.

An exhaustive set of electrolyses performed in the presence of a variety of proton donors made it possible to disentangle the complex protonation–deprotonation steps involved in these experiments. The added proton donors were successively water (1 M), diethyl malonate (5 mM) and, 1,1,1,3,3,3-hexafluoroisopropyl alcohol (5 mM). The

main effect of these proton donors, particularly DEM and HFIP, was to drastically decrease the participation of the dehydrohalogenation of the starting substrate. This effect yielded cleaner final reaction mixtures, although the conjugate base of DEM reacted with the starting substrate to yield the substitution product diethyl 5-decyn-1-ylmalonate. The cleaner medium gave the appearance of an increase in percentage of cyclised product: 42% without any added proton donor, 48% with DEM added and 60% with HFIP. Actually, if one looks at the relative percentages of pentylidenecyclopentane and 5-decyne which gives an idea of the two main fates of the 5-decyn-1-yl radical: cyclisation *versus* reduction, a different trend appears. In the absence of any proton donor the relative yields of pentylidenecyclopentane/5-decyne are higher (42/15) than



Scheme 4

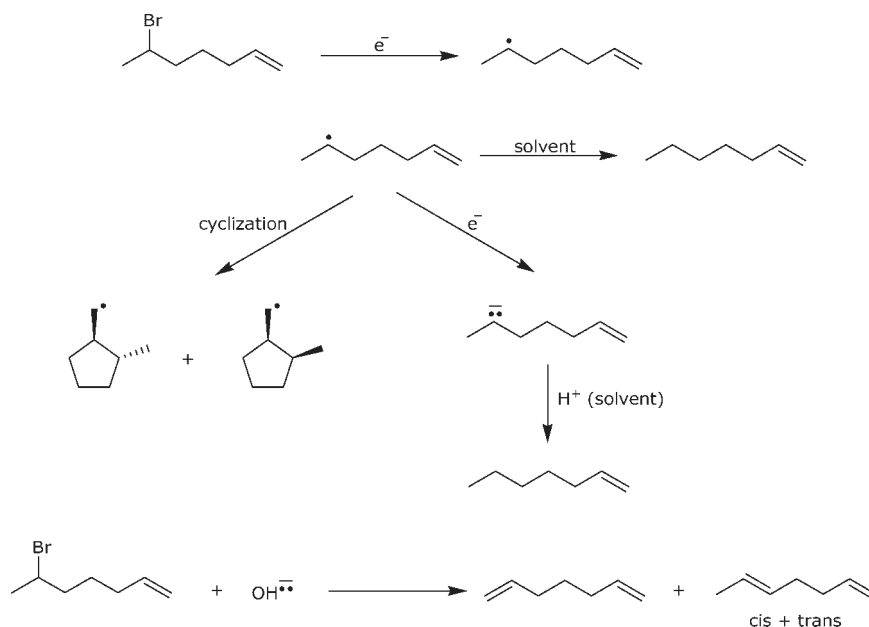
in the presence of DEM (48/23) or HFIP (60/31). Everything goes as if a higher concentration of the carbanion favoured the production of the cyclised product. This point was not discussed in the original report, we will return to it after examining the results of Schmit's PhD.

Schmit's study of 6-bromo-1-heptene. Autocatalytic effect and its possible applications in the rationalisation of evolutions of yields when Grignard reagents are formed from alkyl halides

Schmit, in a PhD never published in the current literature, studied in detail the electrochemical reactivity of 6-bromo-1-heptene to use it as a tool in the mechanistic investigation of the cathodic alkyl aryl ethers cleavage.⁴³ Garst and Hines had previously shown that this radical probe is efficient to distinguish radical intermediates from carbanionic ones. The signature of the radical pathway is provided by a cyclisation where the *cis/trans* ratio is higher than 3, whereas the carbanionic cyclisation yields a ratio lower than 1.⁴⁴ Schmit used Pt, C and Hg electrodes. We do not describe the results obtained with Hg electrodes because these electrodes are known to interact specifically with alkyl radicals.^{30,45}

At a platinum cathode (-2.61 V vs. NHE), a solution of the secondary halide 6-bromo-1-heptene in dimethylformamide with the supporting electrolyte tetra-*n*-butylammonium perchlorate (0.2 M) undergoes a controlled potential electrolyse to yield a series of products rationalised according to Scheme 5.

With this cathode, the dominant product was 1-heptene (48%). This product could result, either from the S_{H2} reaction of the 6-hepten-2-yl radical with the solvent or

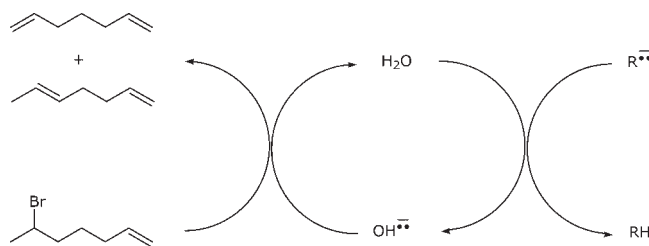


Scheme 5

with the supporting electrolyte, or from the protonation of the heptenyl carbanion formed by the reduction of the heptenyl radical. No isotopic labelling experiments were performed to evaluate the proportion S_{H2} versus protonation. The electrolyses performed at Hg cathode suggest, however, that protonation of the carbanion dominates.

Second in importance were the heptadienes (26%). These heptadienes comprised 1,6-heptadiene and *cis* and *trans*-1,5-heptadienes. These dienes were formed by a deshydrohalogenation of the starting substrate reacting with traces of hydroxide anion. The hydroxide anion originated from traces (1 mM) of water present in the solvent⁴⁶ reacting with the heptenyl carbanion or with the cathode. The reaction could be catalytic as shown in Scheme 6; thus, traces of water left in the solvent were sufficient to effect good quantities of this deshydrohalogenation.⁴⁷ This would be also favoured because, in dimethylformamide a polar aprotic solvent, S_N2 and E2 processes display high rate constants when performed with an oxygen centred nucleophile.

An efficient way to prevent this deshydrohalogenation was to add diethyl malonate (27.4 mM) to the solution.⁴⁸ This reagent would prevent the formation of hydroxide



Scheme 6

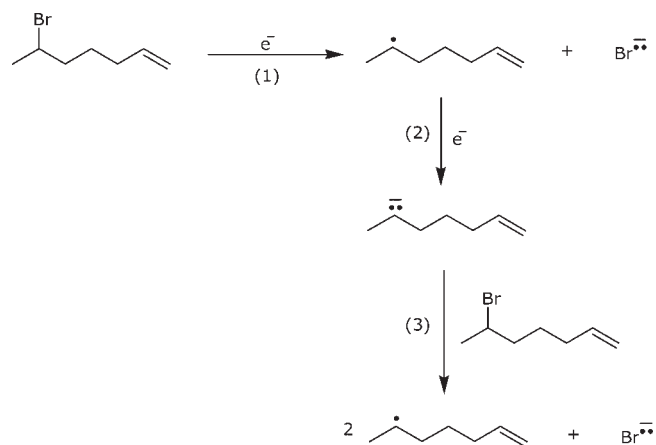
anion. The formed diethyl malonate carbanions are far less reactive in the dehydrohalogenation reaction. Therefore, on a carbon cathode (-2.26 vs. NHE), Schmit was able to totally suppress the production of these dienes by addition of diethyl malonate. A consequence of this addition was the production of an amazing amount of 1,2-dimethylcyclopentane (77%). This product resulted from a radical cyclisation as shown by the large value of the *cis/trans* ratio (3.8). The very high yield of cyclised product under these conditions suggests a double role for the added diethyl malonate. Besides avoiding the presence of the hydroxide anion, this additive could act as a mediator for redox catalysis. We will see, with 6-bromo-1-heptene, that electrolysis under redox catalytic conditions increases the yield of cyclised products. A more speculative hypothesis would be that the hydroxy anion, when present, attacks the proton α to the radical centre of the 6-hepten-2-yl radicals at diffusion controlled rate.⁴⁹ This reaction would then compete with the radical cyclisation; DEM would suppress this competition. On the platinum electrode and, without diethyl malonate added, the percentage of 1,2-dimethylcyclopentane was only 19% and on the carbon electrode 50%. With the platinum cathode, using water as proton donor (138 mM) increased the quantity of formed heptadienes from 26% to 77% and decreased that of 1,2-dimethylcyclopentane from 19% to 11%. Schmit proposed that, in this experiment, the reduction of water on platinum became a major reaction pathway increasing, therefore, the percentage of deshydrohalogenation. The decrease of 1,2-dimethylcyclopentane percentage followed from the smaller amount of substrate available because of its consumption in the deshydrohalogenation reaction. This smaller amount of substrate caused also the decrease of 1-heptene percentage from 48% to 12%.

Besides these products, this author identified the presence of 2-heptene (*cis* and *trans*) characteristic of the intervention of a 6-hepten-2-yl anion intermediate.⁵⁰ On the carbon cathode, the effect of adding diethyl malonate to the medium on the quantity of formed 2-heptene was far smaller (increase from 5 to 7%) than the one observed for the deshydrohalogenation reaction. On the platinum cathode, adding water up to a concentration of 138 mM caused a decrease of 2-heptene percentage from 7% to traces. The author considers that the heptenyl anion results from the reduction of the 6-hepten-2-yl radical at the electrode surface. The rate constant of this reduction is low in comparison with the rate constant of the reduction of an aryl radical. Savéant has proposed that this slowness is to be connected with the structural reorganisation from planar to pyramidal and from solvent reorientation.^{38,51} The reduction potential of alkyl and aryl radical recently computed by theoretical methods converge with this conclusion.³¹

No products resulting from the dimerisation of radicals were reported, possibly because of the low concentration of substrate (around 10 mM).

The rate constant of cyclisation of the 6-hepten-2-yl radical is 10^5 s^{-1} at 20°C .^{52,53} Supposing that the competition between the cyclisation of the heptenyl radical and its reduction to the heptenyl carbanion rules the relative yields of dimethylcyclopentane, and 1-heptene plus 2-heptene, Schmit evaluated the upper limiting value for the rate constant of reduction of the 6-hepten-2-yl radical by the cathodes. The approximation was to consider that 1-heptene is exclusively formed via protonation of the heptenyl carbanion when it is known that part of it could be produced by hydrogen atom transfer to the heptenyl radical.⁵⁴ Comparing the ratio of dimethylcyclopentane to the sum of 1-heptene and 2-heptene provided, therefore, an approximation of the relative rates of cyclisation and reduction of the heptenyl radical for a given cathode. This ratio is about 1 to 3 on the platinum cathode whereas for the carbon cathode it is 5 to 1. Taking the reaction layer as 10 \AA thick, yielded rate constants for the heterogeneous ET to the 6-hepten-2-yl radical: $3 \times 10^{-2} \text{ cm s}^{-1}$ for the platinum cathode and $2 \times 10^{-3} \text{ cm s}^{-1}$ for the carbon one. In terms of standard rate constants these values, respectively, convert to $1 \times 10^{-13} \text{ cm s}^{-1}$ and $7 \times 10^{-12} \text{ cm s}^{-1}$. These values are within the range of those more precisely obtained by Savéant's group for the reduction of *sec*-butyl radical on carbon electrodes.⁵¹

The cyclic voltammograms of 6-bromo-1-heptene ($6.7 \times 10^{-3} \text{ M}$ in 0.2 M tetra-*n*-butylammonium perchlorate/DMF) on vitreous carbon electrode revealed an interesting phenomenon. A single, irreversible reduction wave was observed with a peak reduction current at -2.25 V vs. NHE for the first scan. This scan is characterised by the presence of current cross-over (-1.96 V), irregularities in the current, and enhanced current magnitude relative to subsequent scans. The presence of current crossing indicates that a reducible species is being produced during the anodic scan. These types of crossing in the CV traces can indicate that an autocatalytic process (Scheme 7) is taking place for the studied halide under the conditions of study.⁵⁵



Scheme 7

In this mechanism, steps 1 and 2 take place at the electrode, step 3 takes place when the carbanion diffuses away from the cathode or when the alkyl halide diffuses from the bulk toward the electrode. Schmit also observed such a pattern of reactivity with the Hg cathode but not with the platinum one. It leads to higher concentrations of radicals produced relatively far from the cathode and therefore to a higher relative yield of dimethylcyclopentane. One would like to have an evaluation of the rate of step 3 when carbanions are the donors which provide the electron. If this evaluation were to be done via Marcus equation, the high values of the reorganisation energy term λ both for the oxidation of carbanions and the reduction of alkyl halides could lead to some scepticism about the possible occurrence of a rapid ET.^{56,57} Indeed the reorganisation for the autocatalytic reaction could be estimated as the mean between the reorganisation terms related to each self-exchange reaction (reduction of the alkyl radical by the alkyl anion and reduction of the alkyl halide by the radical + halide adduct, respectively). It should then contain the high reorganisation subsequent to the radical to anion transformation and the reorganisation for the dissociative reduction of the alkyl halide. The former term is at least four times the value obtained from the electrochemical standard free energy of activation and is expected to be at least about 2.4 eV.⁵¹ According to Savéant's model of the dissociative ET, the latter term should contain a major contribution from the carbon-halogen bond dissociation energy and might be estimated as at least 3.6 eV for *sec*-BuBr. A total reorganisation energy of at least 3 eV is expected and a value of 3.6 eV was estimated from alkyl halides giving rise to stable anions.⁵⁵ With such high reorganisation energies, the autocatalytic reaction rate at zero driving force could be estimated as $k_{\text{auto}}^0 = Z_{\text{hom}} \exp(-F\lambda/4RT)$ and is of the order of 4×10^{-2} to $10^{-4} \text{ M}^{-1} \text{ s}^{-1}$ for both reorganisation energy values when the homogeneous frequency collision is taken as $3 \times 10^{11} \text{ M}^{-1} \text{ s}^{-1}$. One may remember, however, that if Kornblum had known how to apply the Marcus equation, he would never have dared to propose the famed scheme of chain reactions induced by an ET from a carbanion to a benzyl halide ($\text{S}_{\text{RN}}1$).⁵⁸⁻⁶¹ One had to wait 35 years to have an explanation provided by electrochemists for the thermal version of this reaction.⁶² It is therefore difficult, at this point, to be more quantitative than Schmit was in his PhD.

The autocatalytic mechanism could, possibly, be encountered in the reduction of alkyl halides by metals for the most oxidising alkyl halides (iodides and particularly tertiary iodides)³⁰ whose reduction gives birth to radicals of medium oxidising ability (ramified vs. linear alkyl radicals for example). Indeed, if the oxidising power of the radical is too low, step 2 will be too slow to produce high concentrations of carbanion. If its oxidising power is too high, the reducing ability of its conjugate carbanion will be too low to allow a reasonable rate for step 3. Guo's group quantum-chemically predicted the absolute standard poten-

tials of diverse free radicals in acetonitrile. The E^0 values (vs. NHE) of the phenyl, methyl, ethyl, *iso*-propyl, *tert*-butyl radicals were, respectively, calculated to be -0.60 , -0.98 , -1.55 , -1.81 , -1.88 V .³¹ This trend in the set converges with direct electrochemical characterisation of the radical^{29,32,37,51,63} (0.29 , -0.68 , -1.12 , -1.2 and -1.31 V are found, respectively) and also with indirect characterisation by electrochemical experiments involving redox catalysis⁶⁴⁻⁶⁶ (-0.95 , -1.40 , -1.48 and -1.53 V are proposed, respectively, for these alkyl radicals).

The autocatalytic reaction corresponds to:



in the case of R = alkyl or



when R is a phenyl. From a thermodynamic point of view, its driving force, ΔG^0 , is given by $\Delta G^0 = -F(E_{\text{RX}}^\circ - E_{\text{R}^\bullet}^\circ)$ where E_{RX}° is the standard reduction potential leading to the concerted ET ($\text{R}^\bullet + \text{X}^-$) in the alkyl case or to the formation of the radical anion in the case of aromatic compounds, and $E_{\text{R}^\bullet}^\circ$ is the standard reduction potential of the radical.

Values of E_{RX}° for the concerted ET of alkyl halides are obtained from the electrochemical investigations or from thermodynamic cycles, they are about -0.84 , -0.95 , -1.03 , -0.81 and -0.69 V versus NHE for *n*-BuI, *n*-BuBr, *n*-BuCl, *sec*-BuBr and *tert*-BuBr, respectively.⁶⁷ They are always much more positive than the reduction peak potentials observed by cyclic voltammetry (for example compare $E_{\text{RX}}^\circ = -0.95$ and $E_{\text{p}} = -2.61 \text{ V}$ vs. NHE for *n*-BuBr) as the reduction at the electrode reflects the large reorganisation due to the carbon-halogen bond breaking that accompanies the ET step.^{67,68} The kinetic rate constant of the autocatalytic reaction is a more amenable quantity. It is difficult to estimate but it is expected to increase with the driving force of the reaction.

The highest E^0 value is obtained for the phenyl radical and concomitantly E_{RX}° are always lower than -0.5 V . The occurrence of the autocatalytic path during reduction of aryl halides or formation of Grignard reagent with aryl halides is then greatly thermodynamically disfavoured. In the set of the alkyls, the methyl radical is the strongest alkyl oxidant; therefore, its conjugated reductant, methyl carbanion would be the weakest reducing agent. The strongest reductant would be the *tert*-butyl carbanion. The proposed E^0 values are in the range of the reduction potential of the corresponding alkyl bromides. The driving force for the autocatalytic reaction is then less negative when going from the alkyl iodides to the alkyl bromides to the alkyl chlorides. The occurrence of the autocatalytic path is then more favoured in the order $\text{RI} > \text{RBr} > \text{RCl}$. Finally, the alkyl carbanions are generally strong bases ($\text{p}K_{\text{a}} > 44$ in DMSO).⁶⁹ On one side, this increases their ability to transfer electrons.⁷⁰ But, on the other side, they should be extremely short

lived in the presence of proton donors such as DEM ($pK_a = 16.4$ in DMSO). The autocatalytic mechanism is then likely restricted to a thin layer close to the electrode surface. It would then be difficult to observe this mechanism at the time scale of cyclic voltammetry (0.1 V/s).

This autocatalytic mechanism could, if it occurs, provide a fresh view on facts reported independently from Schmit's studies.

In the paragraph relating the effect of added proton donors on electrochemical cyclisation of 1-iodo-5-decyne, everything went as if a higher concentration of the carbanion favoured the production of the cyclised product. It could be that, in these experiments, an unnoticed autocatalytic process develops under specific conditions. If such is the case, the quantity of 5-decyn-1-yl radicals would be increased and more cyclised product could form.

With respect to the Grignard reagent formation, it is well known that alkyl iodides are the most reactive toward magnesium; nevertheless they generally give the lowest yields in the alkyl halide series iodo, bromo, chloro.¹⁸ It could be that the reason for such a pattern of reactivity is that iodo derivatives, being the best oxidants in this homologous series, are the ones which are the most prone to enter in the autocatalytic cycle. In Kharasch's monography there is a special paragraph concerning the rate of addition of the halide to be adopted for obtaining an optimum yield. It reads 'In general, however, relatively slow addition is to be recommended for iodides, most bromides and a few of the more reactive chlorides'.¹⁸ With a slow addition, the concentration of the halide is obviously minimised as well as the autocatalytic process which gives birth to most of the secondary products. Gilman's group systematically studied how the rate of halide addition affects Grignard reagent yields. The largest differences in yields between the slow rate and rapid rate of addition were mostly observed for alkyl iodides.⁷¹ In contrast, for a considerable number of alkyl and aralkyl chlorides, there was little or no significant difference in the yields of organomagnesium chlorides between the slow addition and rapid addition experiments.⁷¹ For the preparation of *t*-butylmagnesium chloride, however, it was stated that the slower the addition, the higher the yield.⁷² This may be understood if one remembers that the *tert*-butyl carbanion displays the best reducing properties in the alkyl series. This new proposition would complete the more classical ones based on the formation of Wurtz type by-products.^{73,74}

In the same spirit, we observed leaving group effects in the ratio cyclised/uncyclised products when endo-5-(2'-haloethyl)-2-norbornene reacts with magnesium.⁵ A simple mechanism of the type displayed in Scheme 2 would suggest that this ratio must be independent of the nature of X when the MgX^\bullet radicals are supposed to stay at the metallic surface.¹⁶ Nevertheless, we observed that

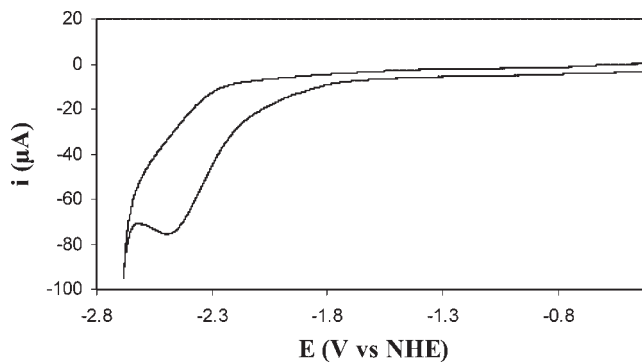


Figure 1. Cyclic voltammogram of the reduction of 8.2 mM solution of 6-bromo-1-hexene in DMF + 0.1 M NBu_4BF_4 (20°C) at 0.1 V/s at a 3 mm diameter glassy carbon disk electrode.

the relative yields of cyclised products decreases in the order $I > Br > Cl$. This observation confirmed Walborsky's group reports on cyclopropyl substrates.⁷⁵ The autocatalytic rationalisation was considered in none of these two reports. It could bring a fresh interpretation of these facts.

Electrochemical behaviour of 6-bromo-1-hexene

We recorded the cyclic voltammograms (0.1 V/s) of an 8.2 mM solution of 6-bromo-1-hexene in DMF (0.1 M, NBu_4BF_4). The reduction demands cathodic potential (-2.49 V vs. NHE) and the voltammograms display a wide peak with a half-width at half-height of 220 mV (Fig. 1) corresponding to the exchange of two electrons per RX. The potential of the reduction peak decreases with the scanning rate ν (Fig. 2) with a slope of 100 mV per decade of scan rate.

These curves can be regarded as driving force (E_p) – activation ($\log \nu$) relationships and an apparent ET coefficient, $\alpha_{app} = \partial \Delta G^\ddagger / \partial \Delta G^0$ can be deduced.^{67,68,76} The apparent transfer coefficient accounts for the

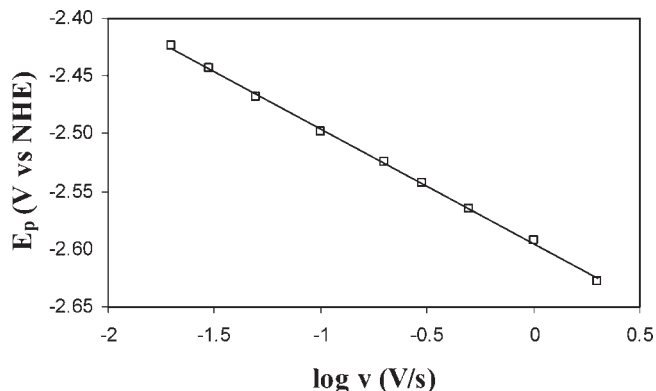
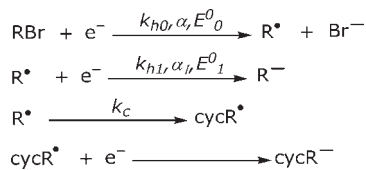


Figure 2. Reduction of a 8.2 mM solution of 6-bromo-1-hexene in DMF + 0.1 M NBu_4BF_4 (20°C). Variations of the the pic potential, E_p , with the logarithm of the potential scan rate, ν .



Scheme 8

importance of the driving force (the potential) on the kinetics of the reduction. Values of α lower than 0.5 indicate that the electrochemical process is kinetically controlled by the ET step which intervenes under a strong driving force. The lower the α value and the higher the energy involved in the ET. On the other hand, values higher than 0.5 indicate that the ET is not the rate limiting step of the reductive process but that it is competing with a following chemical step. Therefore, regarding the reduction of RX, when α is higher than 0.4, it is admitted that the ET and the bond breaking occur sequentially and that the radical anion $\text{RX}^{\bullet-}$ is formed upon the first ET. For values of $\alpha < 0.4$ the ET is accompanied by a large reorganisation of the molecule. In the case of the reduction of RX, when $\alpha < 0.4$ the RX bond breaking is concerted with the ET. The ET is then called dissociative.

The experimental characteristics of the 6-bromo-1-hexene reduction yields a value of $\alpha_{\text{app}} = 0.29$ or 0.21 using, respectively, Eqns (1) and (2):^{67,68,76}

$$\alpha_{\text{app}} = -\frac{RT \ln 10}{2F} \left(\frac{\partial E_p}{\partial \log v} \right)^{-1} \quad (1)$$

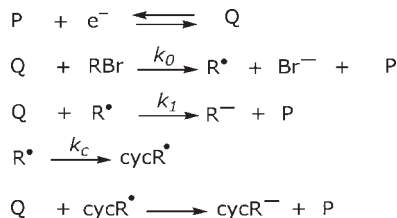
and

$$\alpha_{\text{app}} = \frac{1.85 RT}{F(E_{p/2} - E_p)} \quad (2)$$

These voltammograms are very similar to those reported for *n*-bromobutane ($E_{p, 0.1 \text{ V/s}} = -2.61 \text{ V}$ and $\alpha = 0.3$).²⁹ The mechanism of reduction of 6-bromo-1-hexene suggested by these experiments is shown in Scheme 8.

The first ET is a dissociative ET. The second one has been shown to also be slow because of the reorganisation needed to pass from the radical to the carbanion.⁵¹ Therefore, even if E_1^0 is more positive than the reduction potential of RBr ($E_p = -2.49 \text{ V vs. NHE}$) the reduction of the radical R^\bullet should occur at potentials far more reductive than E_1^0 . The characteristics of the reduction of *n*-butyl radicals have been evaluated to be $\leq -1.06 \text{ V versus NHE}$, $\log k_{h1} = -11.78$ and $\alpha_1 = 0.28$. The reduction of 5-hexen-1-yl radicals should display similar characteristics.⁵¹

When 3.8 mM of 4,4'-dipyridyl (P, $E_{P/Q}^0 = -1.57 \text{ vs. NHE}$) are added to a DMF solution of 6-bromo-1-hexene (8.2 mM), the reduction of this redox mediator loses its reversibility. This shows that, despite the rather different reduction potentials of these two compounds, the radical anion of 4,4'-dipyridyl (namely Q) is able to induce the reduction of the radical probe according to Scheme 9.



Scheme 9

Most of the controlled potential electrolyse experiments were conducted at constant current or constant potential between a graphite cathode and a magnesium anode, both in DMF, THF, ACN and HMPA.

The obtained results are gathered in Table 1. The results obtained in THF (entries T1–T5) show that the amount of cyclised products is slightly higher in the electrochemical experiment than in the reaction between 6-bromo-1-hexene and magnesium in the same solvent (see Bickelhaupt's and Ashby's paragraphs). This is not related to the presence of diethyl malonate in the electrochemical experiments (see Peters' and Schmit's paragraphs). Indeed, entry T3 shows that the same amount of cyclised product is obtained in the absence of this additive. Entry T2 shows that the formation of dimer critically depends on the concentration of the radical probe. This result converges with Peters' report on 1-iodo-5-decyne (see Peters' paragraph). Entries T4 and T5 show that the nature of the cathode is not crucial with respect to the quantity of cyclised product. Entry T10 is important: it shows that the magnesium anode in the presence of 6-bromo-1-hexene at the concentration in THF used in the electrochemical experiments does not react if C and Mg electrodes are not electrically connected. This indicates that the Grignard reaction does not proceed upon 12 h with our experimental set-up. The results of the electrolyses are, then, only due to reduction steps at the cathode and not at the magnesium surface. In ACN (entry A), DMF (entries D1, D2), and HMPA (entry H) more cyclised product is formed than in THF, but, at this point, viscosity is probably not the only parameter to be considered (see discussion in Bickelhaupt's paragraph).

The cyclisation ratio in THF and HMPA may be compared to those observed by Bickelhaupt and Ashby in Grignard reagent formation from 6-bromo-1-hexene.^{16,77} As it was observed in Ashby's work, cyclisation is more favoured in HMPA than in THF. When comparing the electrochemical and magnesium induction, the cyclisation is more favoured upon electrochemical induction in THF while the magnesium induction favours cyclisation in HMPA.

The comparison of the electrochemical and then magnesium induction of RX reduction could be achieved by the mathematical treatment developed by Garst of the D model.^{78–80} This treatment takes into account diffusion of the reactants in solution and their heterogeneous reaction at the metal surface. It is strictly identical to that generally proposed in mechanistic electrochemistry for

Table 1. Product distributions for electrochemical reductions of 6-bromo-1-hexene (CyR = methylcyclopentane)

Entry ^a	η (cP) ^b	q (C)	RBr (mmol)	DEM/RBr ^c	P (mmol)	Experimental condition ^d	Stoich ^e	Conv (%) ^e	Relative yields (%) ^f		
									hexene	CyR	Dimer ^m
T1 ^g	0.459	90	0.51	1.6	0	5 mA	1.8	100	91	9	0
T2 ^g		170	0.95	2.0	0	15 mA	1.9	99	78	10	12
T3		88	0.47	0	0	-2.8 V	2.2	88	90	10	0
T4 ^h		40	0.56	2.5	0	-2.8 V	1.7	44	89	11	0
T5 ^{h,i}		55	0.51	2.5	0	8 mA	2.2	50	90	10	0
T6 ^j		85	0.56	2.6	0.46	-1.9 V	2.0	79	79	21	0
T7 ^j		20	0.56	2.5	0.48	8 mA	2.0	18	80	20	0
T8 ^j		75	0.55	2.6	0.33	8 mA	2.1	70	69	31	0
T9 ^k		30	0.56	2.6	0.33	8 mA	2.1	26	77	23	0
T10 ^l		0	0.56	0	0	0	0	<0.1	0	0	0
D1	0.794	85	0.43	2.9	0	10 mA	2.1	98	83	17	0
D2 ⁱ		85	0.65	2.0	0	8 mA	1.8	75	81	19	0
D3 ^j		35	0.47	2.4	0.28	8 mA	7	11	65	35	0
H	3.22	110	0.56	2.5	0	8 mA	2.0	100	85	15	0
A	0.341	113	0.56	2.5	0	8 mA	2.1	100	70	30	0

^a Experiments T, D, H and A are performed in 4.5 mL of THF, 5 mL of DMF and 4.5 mL of HMPA or ACN, respectively.

^b Viscosity of the solvent in centipoises.

^c DEM: diethyl malonate, when omitted, for T3, 3 eq. of water was added.

^d Electrolysis were conducted at constant current or constant potential between a graphite cathode and a magnesium anode unless otherwise stated; values of the applied variable is indicated.

^e Calculated from coulometry and evolution of the starting product content along the electrolysis.

^f Obtained from GPC and/or GPC-MS.

^g Average of two experiments.

^h A Pt cathode and a graphite anode were used.

ⁱ A graphite cathode and a Pt anode were used.

^j The electrolysis were performed in the presence of 4,4'-dipyridyl.

^k The electrolysis was performed in the presence of 2,2'-dipyridyl.

^l A test solution of RBr in THF is held overnight in the electrolytic cell where the C and Mg electrodes were not electrically connected.

^m From GPC-MS analysis one dimer is formed but its structure was not established.

the estimation of competition between heterogeneous ETs, diffusion and chemical steps.^{81,82} At first sight, in the special case of radical cyclisation (at rate k_c in s^{-1}) versus radical electrode reduction (at rate k_{el} in $cm s^{-1}$) one predicts that:⁸²

$$\frac{\text{Red}}{\text{cyc}} = \frac{(k_{el}/D)}{(k_c/D)^{1/2}} \quad (3)$$

where D is the diffusion coefficient of the species. This evolution is actually similar to that proposed in the simplest treatment proposed by Garst *et al.*⁷⁸ In this simplest treatment, he showed that $(\text{QMgBr}/\text{RMgBr}) = (k_c \tau_R)^{1/2}$, where QMgBr and RMgBr are, respectively, the cyclised and reduced Grignard products, and τ_R is the lifetime of R^\bullet of the order of 3×10^{-8} s. Under our electrochemical conditions in THF we obtain, $\tau_R = 4.2 \times 10^{-8}$ s ($k_c = 2.3 \times 10^5 s^{-1}$, 25°C) in quite good agreement with the values obtained for other alkyl halides (see for example Fig. 1 in Ref. 78 or Fig. 2 or 3 in Ref. 10).

The parameter defined in Eqn (3) corresponds also to the dimensionless parameter Δ_Q defined in Garst's more refined model where the cyclisation versus reduction competition is complicated by possible occurrence of dimerisation and solvent attack (H-atom abstraction) of

the radicals.⁷⁹ Garst then showed that, when solvent attack is negligible, the problem is described by two composite dimensionless parameters V_Q and Δ_Q :

$$V_Q = \frac{4k_d v}{3k_c^{3/2} D^{1/2}} \quad (4)$$

$$\Delta_Q = \frac{k_{el}}{(Dk_c)^{1/2}} \quad (5)$$

that characterise, respectively, the consumption versus generation of the radicals and the generation versus cyclisation of the linear radical. In these equations, k_d is the dimerisation rate constant and v is the flux of formation of the radical at the metal surface.

The difference between the electrochemical and magnesium induction resides only in the values of V_Q and then only in the flux of radical generation v , that is the flux of alkyl halide consumption. In Grignard reagent formation experiments, it was estimated by Garst of the order of $2 \times 10^{-5} \text{ mol cm}^{-2} \text{ s}^{-1}$.⁸⁰ Under electrochemical induction the equivalent of the flux of RX consumption is the equivalent of the current density and:

$$v = \frac{i}{2FA} \quad (6)$$

where i is the current of the electrolyse, F , the Faraday constant ($F = 96\,500\text{ C}$) and A , the electrode surface area. A flux of RX consumption of the order of $10^{-8}\text{ mol cm}^{-2}\text{ s}^{-1}$ is obtained. It is three orders of magnitude smaller than the fluxes used in Grignard reagent formation. The difference in the reduction/cyclisation ratios observed could be attributed to the difference in the reactant consumption fluxes. Indeed, Garst showed in its complete treatment of the D model that a decrease in the flux of formation of R^\bullet , ν , induced a decrease in the ratio red/cycle.⁸⁰ Moreover, for the electrochemical experiments, from the value of the parameter V_Q it is predicted that no dimer of the cyclised radical should be found, in keeping with the experimental results. For higher concentration of RX and also higher current densities, the dimerisation might occur as observed (Table 1, entry T2).

It is interesting to note that high current density, as those used in Grignard reaction cannot be used by electrochemical means under our specific experimental conditions. Indeed, such high current density would lead to the electrolyte reduction and then to a loss in the reduction selectivity. The increase of the current density within electrochemical induction means the use of higher mass transfer to the electrode. This can be achieved by using either much more efficient stirring, or by reducing the cathode–anode separation distance. Under our experimental conditions the mass transfer is achieved in a diffusion layer of the order of 10^{-3} cm , an increase of three orders of magnitude of the current density corresponds to a diffusion layer 1000 times smaller, of the order of tens of nanometer. Such low distance is not reachable experimentally in electrochemical cells, it is actually achieved within magnesium induction when one considers the corrosion model proposed by Garst. Another alternative to the achievement of higher current densities is the use of electrodes of micrometric size, as it is well known that such ultramicroelectrodes support much higher current densities than conventional millimetric ones.^{83–91} This argument would also be in favour of the special interest in the use of finely divided magnesium particles. One may recall, at this point, that a characteristic shared by metal vapour synthesis experiments and Rieke's activated magnesium, is the very small size of metal particles.^{5,41} Rieke was able to reduce fluoroaromatics with this magnesium when Ashby had failed.^{40,41}

The electrochemical experiments performed via a homogeneous ET mediated by dipyrindyl yield higher yields of cyclised product (entries T6–T9 and D3). This pattern of reactivity is similar to the one observed for the reduction of aromatic radical clocks.^{28,92} It underlines again the higher rate of ET under heterogeneous conditions than under homogeneous ones.

It is difficult to discuss those trends as they compare surface and solution reactions. Indeed, the ratio red/cycle is proportional to $k_c^{-1/2}$ for heterogeneous induction as it should rather be proportional to k_c^{-1} for homogeneous

ones (roughly, one expects that red/cycle $\sim k_{\text{hom}}C_M/k_c$ where k_{hom} is the homogeneous reduction rate of the linear radical, C_M is the solution redox mediator concentration). Moreover, the heterogeneous reaction is performed with a higher driving force than the homogeneous one, as the electrochemical reduction is achieved at a potential of approximately -2.6 V versus NHE while the mediated reaction is performed at -1.57 V and -1.87 V versus NHE for the 4,4'-dipyridyl and 2,2'-dipyridyl redox mediator, respectively. However, the observed reactivities are in good agreement with what could be expected: the more reducing the redox mediator and the higher the radical reduction and the lower the cyclisation. Those trends are also in agreement with the literature as ratio red/cycle < 1 are obtained in DMF with less reducing Ni(I) complexes.⁹³

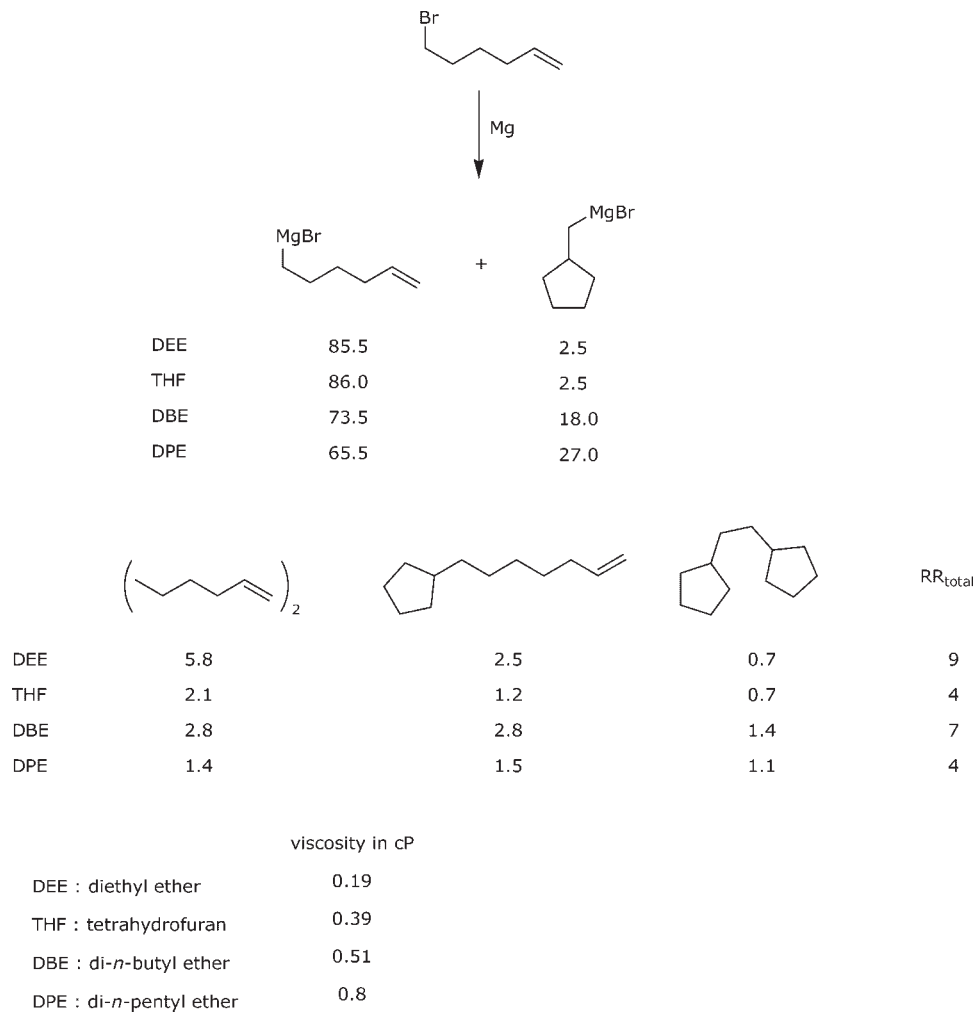
GRIGNARD REAGENT STUDIES INVOLVING ALKYL CENTRED RADICAL CLOCKS

Bickelhaupt's studies of Grignard reagent formation from 6-bromo-1-hexene and CIDNP observations

From 1972 to 1980, Bickelhaupt's group published a series of reports based on the combined study of radical clocks, CIDNP effects, and solvent effects to gain new insights on the mechanism of formation of RMgX ($\text{R} = \text{Alkyl}$).^{12–14,20,77,94–96}

In a typical experiment, about 12 mg of magnesium crystals in a NMR tube were covered with 0.42 mL of dry and deoxygenated solvent, then about 0.13 mL of 6-bromo-1-hexene was added and the tube, closed with a cotton wool plug, was placed in a Varian A-60 NMR spectrometer then the progress of the reaction was continuously monitored.⁷⁷ The concentration range is therefore about 2 M. The analysis of coupling products (RR) was performed by GLC and the one of Grignard compound (uncyclised + cyclised) by acid–base and Complexon III titration. The percentages of the cyclic and open chain Grignard compounds were calculated from the peak areas in the final spectrum.

Scheme 10 gathers the reported results. The most remarkable trend in the data is that solvents of high viscosity favour the formation of cyclised products, although the ratios cyclised/uncyclised remain, in all these experiments, far lower than the ones reported in the reactions of 6-bromo-1-hexene with Bu_3SnH .^{97–100} This observation was rationalised by proposing that these solvents slow down the diffusion of 5-hexen-1-yl radicals towards MgBr^\bullet formed at the metal surface by the reaction of $\text{Mg}^{\bullet+}$ with the bromide anion created by the first ET. That would let them more time to cyclise on their way back to the surface. This explanation is not totally compelling. The first ET being highly dissociative for alkyl halides should create the 5-hexen-1-yl radicals in



Scheme 10

close vicinity to the metallic surface and to $\text{Mg}^{\bullet+}$, a viscous solvent could slow down the diffusion away of this radical and, therefore, favours its reaction with $\text{Mg}^{\bullet+}$ which yields the uncyclised Grignard reagent. One may note that, for this alkyl radical probe, the two solvents DEE and THF yield approximately the same ratio cyclised/uncyclised products. In contrast, for the corresponding aryl radical clock, the less viscous and less polar solvent (DEE) yields clearly the highest amount of cyclised products.⁶

Another rationalisation of the observed results may be offered if the formation of carbanions is considered as a possible fate for the alkyl radical formed in close vicinity of the metallic surface by the dissociative ET to 6-bromo-1-hexene. In a solvent of high viscosity, these carbanions would diffuse away slower from the metal surface. A higher concentration of carbanion could accumulate in the close vicinity of the surface increasing, therefore, the participation of the autocatalytic route (Scheme 7) which yields higher yields of cyclised products. This autocatalytic rationalisation is not necessarily needed. Examining this set of data within the framework of the

D model, Garst obtained a dramatic agreement between experimental and calculated results. In his approach, the simulations suggested that effects of polarity could dominate those of viscosity.⁷

In THF and DEE, the quantities of cyclised 5-hexen-1-yl radical (Scheme 10) were distinctly lower than the ones measured in our electrochemical experiments in THF (Table 1). Several causes could explain this difference.

First, the experiments with magnesium occur in a medium richer in MgBr_2 . The presence of this salt decreases the radical participation in the reaction of aryl halides with magnesium.⁶ However, this effect apparently disappears in the reaction of 6-bromo-1-hexene with this metal although it reappears in the reaction of bromocyclopropanes and could be the basis for the entrainment effects reported with 1,2-dibromoethane.^{101,102}

Second, in the electrochemical experiment, the concentrations of 6-bromo-1-hexene are about one order of magnitude lower than in Bickelhaupt experiments. The controlled potential electrolyses of 1-iodo-5-decyne reported by Peters' group show that higher concentrations of radical probe induce higher proportions of cyclised

product. This is opposite to the displayed trend of data that we presently discuss.

Third, in the corrosion hypothesis applied to Grignard reaction the spatial separation between anodic and cathodic sites is supposed to be rather small.⁷ This could correspond to a highest current density for the magnesium than for the cathode. Wendt discussed the effects to be expected when the current density increases near the metallic surface. The reactions of higher order, for example, radical dimerisations or second order disproportionation reactions are favoured over first or pseudo first order reactions.¹⁰³ Table 1 compared to Scheme 10 shows that more dimerisation products form at magnesium surface than at the studied cathodes. This fact suggests indeed that higher current density is present at the magnesium surface. If it is so, the concentration of radicals produced at the magnesium surface could be higher than at the cathode. Therefore, their rate of reduction by the metal could be higher and the higher proportion of linear product formed in the reaction between magnesium and 6-bromo-1-hexene would be rationalised. This observed trend in formation of dimers is, however, not totally compelling because entry T2 suggests that the difference between electrochemistry and Mg could simply be one in concentrations of RX.

One important aspect of Bickelhaupt's set of studies was the observation of CIDNP effects when the Grignard reaction of various alkyl halides was performed in an NMR spectrometer. The multiplet effects observed in the NMR spectra of RMgX (R = Et, *n*-Pr, *i*-Pr, PhCH₂CH₂) established that, at least part of the Grignard reagent, was formed via alkyl radicals. The difficulty with CIDNP effects is that they did not, at this time, make it possible to decide if this part is small or important.

To rationalise the fact that no net effect was observed in these experiments, the authors proposed that the reaction of R• with XMg• radicals not yet solubilised and formed at the site of ET from the metal to the alkyl halide is the major reaction leading to the Grignard compound. The part of RMgX showing CIDNP effect would result from R• radicals having escaped this major reaction by diffusing away from the metal surface, having met another R• radical to form a radical pair in which the polarisation was settled, having not reacted in the radical pair to yield coupling or disproportionation products and having returned to the metal surface to meet another XMg• having not yet reacted with the R• radical formed in its vicinity.²⁰ This description of the succession of possible events before introducing polarisation in the ¹H-NMR signal of RMgX suggests that the CIDNP effect deals with only a minority of the overall formed RMgX. The direct reaction at the site of ET is by far the most important route leading to the Grignard compound. The authors stressed this point remarking that in the studied reactions the yields of RMgX could be rather high (R = Et, X = Br Yield = 93%; R = Pr, X = I Yield = 86%). If all of the RMgX was formed via alkyl

radical pairs, one would expect a much lower yield of RMgX because loss of radical R• in coupling and disproportionation reactions would be considerable.²⁰

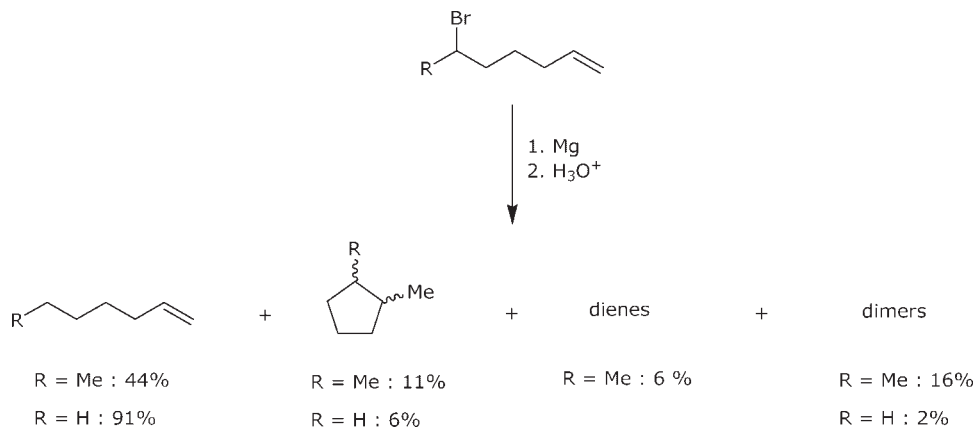
The multiplet effects were also observed in the disproportionation products of R• radicals for R = *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu. This series of studies was the starting point to suggest that most of RMgX was formed from the reaction between R• and MgX• (some authors seeing this last species as fixed on the metal surface, others preferring it as a soluble species). In the most detailed discussion of CIDNP effects, Bickelhaupt states 'ET to radical R• might of course also take place from the metal surface followed by reaction of the carbanion with magnesium halide... Although such an ionic pathway is felt to be less likely in the normal Grignard reaction, it cannot be excluded at this stage'.²⁰ In the same report, reference was made to the work describing the formation of Grignard reagents from the reaction between carbanions and MgX₂.^{104,105} This proposition was, then, no longer discussed in the CIDNP contributions of this group.

The non observation of net CIDNP effects in these experiments contrast with the report describing net effect in the reaction between sodium mirrors and methyl iodide.¹⁰⁶ Taking into account the various progresses made in the models of CIDNP effect interpretations it would be interesting to complete Bickelhaupt's group pioneering studies and gain further information on Grignard reagent formation mechanism.¹⁰⁷⁻¹⁰⁹

Ashby's studies of Grignard reagent formation from 6-bromo-1-heptene and 6-bromo-1-hexene

In 1988, Ashby reported an exhaustive study of the mechanism of Grignard reagent aiming at providing an answer to the question: is RMgX totally formed from radicals remaining adsorbed on the metal surface, or could it be that part of the radicals diffusing away from the metallic surface then return to this surface to yield RMgX?¹⁶ This work was therefore in the line with the controversy A model (Kharasch-Walborsky)^{18,27} versus D model (Garst).¹¹⁰ The provided answer was that, for the studied alkyl radical clocks, 25% at least of RMgX was produced from alkyl radicals which had first diffused away from the metal surface.

Part of the work dealt with the 3 h reaction of 6-bromo-1-heptene in THF at 22 °C with sonication in the presence of bromoethane for entrainment. The identified products, after hydrolysis of RMgBr were 1-heptene (44.3%), 1,2-dimethylcyclopentane (11.2%) with a *cis/trans* ratio characteristic of a radical cyclisation, dienes (6.1%), and dimers (16.1%). In comparison, the same reaction performed under the same conditions with 6-bromo-1-hexene yielded 1-hexene (91%), methylcyclopentane (5.8%), and dimers (1.7%) (Scheme 11).



Scheme 11

Supplementary information was provided because the hydrolysis of the reaction mixtures was performed with D₂O. Then the percent of deuterium incorporation was measured in both the linear products and the cyclised ones. This way, the percentage of 6-hepten-2-yl and 5-hexen-1-yl radicals having reacted via hydrogen abstraction with the medium was known. It was more important for the 6-hepten-2-yl radical (26%) than for the 5-hexen-1-yl one (1.5%). The same trend in hydrogen abstraction was present for the cyclised products: in the reaction with 6-bromo-1-heptene an average of 45%, whereas only 13% for the reaction of 6-bromo-1-hexene. Ashby interpreted these results according to two main hypotheses.

The first one was stressing the importance of diffusive events in settling the selectivity. The reactions competing with the cyclisation of the radicals formed by the first dissociative ET occurring in the close vicinity of the metal would be: (1) reaction with MgBr[•] radicals formed at the metallic surface by the very rapid reaction of Mg^{•+} with bromide anions, (2) reaction with any hydrogen atom donor in the medium or (3) dimerisation. The first reaction, leading to RMgBr, was clearly occurring at the metal surface, either with a carbon centred radical directly formed there, or with a radical which, in a first time, had escaped this vicinity, had survived the events of abstracting a hydrogen atom, dimerisation or cyclisation and had diffused back to the metal surface. The second kind of reactions (cyclisation, atom transfer, and dimerisation) was occurring while the carbon centred radical was diffusing away from the metallic surface, having escaped the immediate recombination with MgBr[•] radicals.

The second, implicit, hypothesis was that the formed alkyl radicals do not react with the metal surface to get reduced into carbanions. This hypothesis was possibly a consequence of the Prevost–Anteunis controversy.^{111,112} Prevost had proposed, in 1959, that the reaction between magnesium and alkyl halides directly produced carbanions and that these carbanions reacted with the cation MgBr⁺ to yield the Grignard reagent. Anteunis criticised

this proposition, stressing the point that Prevost's experimental results could, as well, be rationalised by a mechanism involving radical species. Prevost then published a series of contributions where the results were, this time, rationalised with a mechanism involving radicals.¹¹³ For 20 years, no carbanionic species were involved in the various mechanistic proposals for the Grignard reagent mechanism of formation, up to the Bickelhaupt's results on the aromatic halides.^{1,114}

Within Ashby's framework, the sharp increase of hydrogen abstraction when passing from the 5-hexen-1-yl radical to the 6-hepten-2-yl radical, was seen as a direct result of the 6-hepten-2-yl greater stability and higher steric hindrance. These two factors would converge to diminish the probability of an immediate recombination with MgBr[•] radicals. Therefore, a higher percentage of 6-hepten-2-yl radicals were expected to diffuse toward the bulk of solution. During this diffusion they could undergo cyclisation, hydrogen atom transfer, or dimerisation; henceforth both the increased yields of hydrogen abstraction and cyclisation when passing from 6-bromo-1-hexene to 6-bromo-1-heptene could be understood. One may remark at this point that Garst, in his D model does not specify that the route from the having diffused alkyl radicals to RMgX necessarily implies a reaction between these alkyl radicals and MgX[•].⁷ The intervention of MgX[•] is a precision introduced by Ashby. Implicitly, this author admits a far higher rate constant for the reaction of an alkyl radical with MgX[•] (coupling reaction) than for its reaction with metallic magnesium (one-electron reduction). Indeed, in the D model, the alkyl radicals having escaped the surface have a good probability to reencounter it.⁷ But, at the point of reencounter the probability of meeting a zerovalent magnesium atom is far higher than meeting an MgX[•] group. Therefore, if one wants to discard the one-electron reduction pathway, one has to compensate this higher probability by an intrinsic far higher rate constant for the coupling reaction.

Let us slightly modify Ashby's leading hypothesis. Suppose, within the organic corrosion approach^{7,10} and,

in line with electrochemical experiments described previously, that, in the reactions competing with the cyclisation, we replace the recombination with MgBr^\bullet radicals by a second ET from the metallic surface to the carbon centred radical. This would lead to a carbanion which would go to RMgBr by reaction with MgBr_2 . This time, the results discussed in the preceding paragraph would simply follow from the fact that the 5-hexen-1-yl radicals (primary radicals) are easier to reduce than the 6-hepten-2-yl ones (secondary radicals).^{31,115} These primary radicals being faster reduced at the metal surface have a smaller probability to diffuse away and to undergo atom transfer, cyclisation or dimerisation. Eventually, the carbanions have to travel in the solution to meet MgBr_2 formed at an anodic site spatially separated from the cathodic one (corrosion model of the Grignard reagent formation).^{7,10}

Within the same spirit, one has to compare the pattern of reactivity observed for 6-bromo-1-heptene and 6-bromo-1-hexene reacting with a cathode or reacting with metallic magnesium. Schmit's results compared to ours at a carbon cathode show that, in DMF, more cyclisation is observed for 6-bromo-1-heptene than for 6-bromo-1-hexene (50% vs. 18%). As the rate constant of cyclisation the 6-hepten-2-yl radical is half that of the one measured for the 5-hexen-1-yl radical, this result could appear as unexpected.^{53,100,116} On the other hand, primary radicals are easier to reduce than secondary ones. Therefore, the reduction reaction, which competes with the cyclisation, should be faster for the 5-hexen-1-yl radical than for the 6-hepten-2-yl radical.

The trend 'higher formation of cyclised compound for 6-bromo-1-heptene than for 6-bromo-1-hexene' is also displayed in the formation of Grignard reagent (11.2% vs. 5.8% in Ashby's results). Our electrochemical experiments with 6-bromo-1-hexene compared with those obtained by Bickelhaupt in the formation of Grignard reagent showed that more cyclisation occurs at the cathode than at the magnesium surface. This trend is also met for 6-bromo-1-heptene (50% vs. 11%). Again everything goes as if the magnesium surface was displaying a higher reducing activity than the cathode.

The sonochemical activation of magnesium used by Ashby could have perturbed the results of selectivity. Nonaka has shown that sonochemistry may dramatically change the selectivity of ET reactions where transport phenomena play a role and similar observations are reported in normal sonochemistry.^{117,118} Nevertheless the percentages of cyclisation reported by Bickelhaupt and Ashby in THF are remarkably similar (around 5%).

CONCLUSIONS

This report compared the patterns of reactivity of a variety of alkyl radical clocks at cathodes and in their reactions with magnesium to form Grignard reagents. The aim of

this comparison was to determine which main reaction competes with the cyclisation of the radical probes. Up to now, the main current of thought on this question had been that alkyl radicals couple with MgX^\bullet radicals to yield RMgX . A noticeable exception to this main trend was Garst's formulation which preferred the formation of RMgX via alkyl carbanions. The electrochemical experiments clearly yield mixtures of carbanions and radicals at the cathode when alkyl halides are electrolysed. They, therefore, provide a benchmark for looking at the trends to be expected in terms of selectivity when carbanions are formed from alkyl halides. The comparisons in this report show, that the same radical clocks display amazing similarities when opposed to cathodes or to magnesium.

There are differences, however. Apparently, if the carbanionic hypothesis were to be extended to the Grignard reagent formation, one would have to rationalise the observation that the magnesium surface appears as a better reducing agent than cathodes. A double explanation could account for this observation. First, the small size of magnesium particles increases the surface of contact with respect to a classical cathode. Second, the magnesium behaviour would be better compared to what occurs at microelectrodes. More work is needed in this direction.

If the Grignard reagent formation is considered in an electrochemical perspective and going through carbanionic species, some consequences in terms of selectivity may be proposed. For a given R in the alkyl halide, the highest production of radicals (lowest yields in RMgX) should be expected for the iodides despite the fact that they are the best electron acceptors. This could have two reasons. The first would be that at the potential where RI is reductively dissociated, the reduction of the formed radicals into carbanions is relatively slow, the worst case being for the tertiary radicals formed from the reductive cleavage of RI.

Indeed, from an electrochemical point of view, the formation of Grignard reagents on magnesium surfaces is similar to a constant current electrolysis. Therefore, the reduction potential of the magnesium surface is dictated by the current-potential curve and should adjust itself depending on the values of the current density involved in the reduction and the mass transfer rate of reactant arrival at the electrode. If this current density is small compared to the maximum mass transfer rate of arrival of RX at the magnesium surface, the reduction potential of the magnesium surface should set at a potential close to the reduction potential of RX and one could trigger the R^\bullet reduction occurrence. One could then imagine reduce selectively RI and not R^\bullet . In the reverse condition the reduction potential of the magnesium surface could set at the reduction potential of the worst electron acceptor and one could lose the reduction selectivity.

The second reason, more speculative, would be that autocatalytic processes would have more chances to develop for these iodo substrates. At the other end of the

spectrum of possibilities, the chlorides would behave just in the opposite way because at the potential at which they accept the electron, the radicals formed by their dissociative reduction would be ready to be transformed into carbanions. On the other hand, they are poor candidates for the autocatalytic process. Extrapolating this trend one would guess that the best candidates for excellent yields of RMgX (alkyl) formation would be the alkyl fluorides. These Grignard reagents have resisted direct preparation for decades but Ashby and then Riecke could obtain them when using highly activated forms of Mg. We, indeed, have shown for aluminium that using planning of experiment methodology to optimise the Riecke's concept of active metal slurries, quantitative yields for the reduction of p-fluorotoluene could be reached, this substrate being famed for its resistance to metal powder reducing agents.¹¹⁹ The optimisation of reaction conditions could provide the counter intuitive result that they are the best candidates for excellent yields in RMgX preparation.

EXPERIMENTAL PART

Chemicals

The different solvents (THF, DMF, ACN, HMPA) were puriss absolute anhydrous solvents from commercial origin (Fluka, St Quentin Fallavier, France) and used as received. 6-Bromo-1-hexene was obtained from Aldrich. NBu_4BF_4 was synthesised from ammonium tetrafluoroborate and tetrabutylammonium chloride (Fluka, France) and recrystallised in petroleum ether then dried overnight before use.¹²⁰ Samples of 6-bromo-1-hexene, 1-hexene, and methylcyclopentane were obtained from Aldrich (St Quentin Fallavier, France).

Cyclic voltammetry

The working electrode was a 3-mm diameter glassy carbon disk. It was carefully polished and rinsed in ethanol before each voltammogram. The counter electrode was a platinum wire and the reference electrode an aqueous SCE electrode. All potentials were then shifted so as to be reported *versus* NHE knowing that: E (vs. SCE) = E (vs. NHE) - 0.24 V. Cyclic voltammograms were recorded using a CHI660A potentiostat (CH Instruments, IJ Cambria Scientific, Burry Port, UK).

Electrolysis

Direct or mediated electrolyses of 0.1–0.2 M solutions of 6-bromo-1-hexene, containing 0.1 M NBu_4BF_4 degassed by argon, were undertaken under constant current or constant potential in the presence of a weak acid

(2 equivalents of diethyl malonate) in THF, DMF, ACN or HMPA. They were carried out in an undivided cell containing 4–5 mL of solution. The electrolysis was performed in a cylindrical glassy-carbon crucible of 20 mm diameter and 20 mm height that was used as working electrode or counter-electrode. The counter electrodes were: (i) a soluble anode consisting of a cylindrical magnesium rod of 8 mm diameter, or (ii) the glassy carbon crucible, or (iii) a Pt electrode of area 2 cm^2 . The working electrode was either the glassy carbon crucible or a Pt electrode of area 2 cm^2 . The electrolyses were conducted at constant potential (referred to aqueous SCE, CHI660A potentiostat) or constant current (constant current generator) and controlled by coulometry. Aliquots of $100\ \mu\text{L}$ of solution were extracted regularly, passed through silica column chromatography without acidification, and analysed by GC in order to check the course of the reaction. Finally, the last aliquot of the electrolysed solution was analysed by GC-MS, for detection of possible coupling products.

GC analysis were performed with a Varian 3700 equipped with a FID using a 30 m DB-wax capillary column (inner diameter: 0.25 mm, film thickness: $0.25\ \mu\text{m}$) with a programmed temperature ($35\ ^\circ\text{C}$ for 3 min, rising $25\ ^\circ\text{C}/\text{min}$ to $220\ ^\circ\text{C}$ for 5 min).

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