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TUTORIAL REVIEW

The frequently overlooked importance of solvent in free radical syntheses

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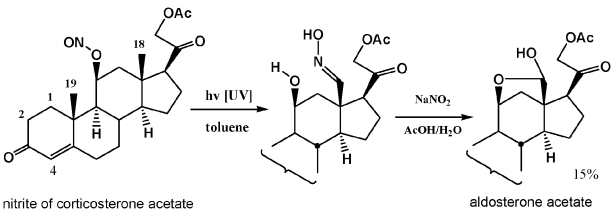
This *tutorial review* is designed to dispel the myth, still believed by many synthetic organic chemists, that radical-based syntheses are free from significant solvent effects. However, many synthetically valuable radical reactions do exhibit large kinetic solvent effects. It is therefore important to select the solvent for any proposed radical synthesis with considerable care if good product yields are to be achieved.

There is a growing awareness of the important role that free radicals can play in organic syntheses.[1–6] A frequently stated advantage of radical-based methodologies for molecular constructions is that radical reactions are essentially free from solvent effects on their reaction kinetics and, hence, on the reaction products. The potential roles that solvents can play in syntheses have usually been ignored or cursorily dismissed, *e.g.*,[7] "Major effects that solvents can have on rates of ion–molecule reactions are eliminated" (in radical reactions). Chemists who uncritically accept this conventional wisdom may suffer serious disappointments when they attempt to transfer some "known" radical reaction to a solvent different from that originally employed. Such a change in solvent may be dictated by considerations such as toxicity, or cost, or more usually, by the low solubility of the new reactant in the original solvent. However, solvents can have dramatic effects on the kinetics of many radical reactions. Such kinetic solvent effects, KSEs, can, for example, greatly reduce the rate of a radical chain reaction and can even cause a planned reaction to follow an unwanted and unexpected pathway. It is the purpose of this tutorial review to alert synthetic chemists to the importance of a judicious choice of solvent for their planned radical reactions. A proper awareness of KSEs should eliminate many unwelcome surprises.

Remote intramolecular functionalizations using alkoxyl radicals

Alkoxyl radicals abstract C–H hydrogen atoms extremely rapidly even when the C–H bond is not 'activated'. Barton exploited this fact in his ingenious synthesis of aldosterone by the UV photolysis of the nitrite of corticosterone acetate in toluene at room temperature.[8] The photo-generated alkoxyl radical performs an intramolecular H-atom abstraction from the 18 methyl group and the resulting primary alkyl radical is trapped by the photo-generated nitric oxide to form a C-nitroso compound, which tautomerises to the corresponding aldoxime (21% isolated yield). The aldoxime gave aldosterone acetate (~15%) on treatment with nitrous acid[8] (see Scheme 1). The low yield is partly due to abstraction from the 19-methyl group, the alkoxyl radical being equidistant from both methyl groups, so that H-atom abstraction occurs from both. Nevertheless,



Scheme 1 Barton's aldosterone synthesis.

Grzegorz Litwinienko

Grzegorz Litwinienko received his PhD in chemistry in 2000 from University of Warsaw (Poland). In 2001–2003 he was a Postdoctoral Fellow at the National Research Council in Ottawa (first on a Fellowship awarded by the Foundation for Polish Science and, subsequently, by the Natural Science and Engineering Research Council of Canada). In 2004, he returned to the Faculty of Chemistry at the University of Warsaw where, in 2006, he obtained his DSc (Habilitation). His main research interests are organic free radical chemistry, autoxidation and antioxidants, solvent effects, and supramolecular chemistry.

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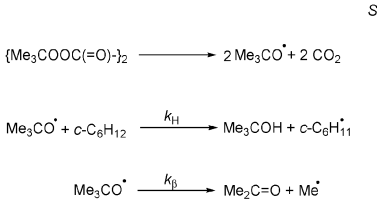
this incredibly short synthesis is the most effective route to aldosterone and yielded a 70 g sample when the world supply was only a few mg.

The generality of this chemistry has been exploited by Barton[9] and others. The intramolecular H abstraction is very sensitive to geometric factors, a fact that has been utilized to improve the synthesis of aldosterone.[10] An essential step in all of this chemistry is the highly efficient trapping of the carbon-centered radicals by the nitric oxide. In the absence of oxygen, alkyl radical trapping by nitric oxide occurs almost exclusively. This is at variance with the usual rule (from gas phase chemistry) that when two radicals $X^{\bullet}$ and $Y^{\bullet}$ are produced at equal rates and form combination products at diffusion-controlled rates, the products, X_2, XY, and Y_2, will be formed in the statistical ratio 1 : 2 : 1. However, solution chemistry has shown that when the rates of: $2X^{\bullet} \rightarrow X_2$ and $2Y^{\bullet} \rightarrow Y_2$ differ appreciably, as is the case when $X^{\bullet}$ is a transient[11] and $Y^{\bullet}$ is a persistent[11] radical, the major (often sole) product is XY.[12–15] This is because the cross combination, $X^{\bullet} + Y^{\bullet} \rightarrow XY$, usually occurs at, or close to, the diffusion-controlled limit. As a consequence, the concentration of $Y^{\bullet}$ quickly builds up to the point that $Y^{\bullet}$ captures all $X^{\bullet}$ before they can undergo any other reaction. This Barton chemistry provides an early example of the Ingold-Fisher Persistent Radical Effect,[13–15] *i.e.*, the primary alkyl radical is transitory ($X^{\bullet}$) while the nitric oxide is an extremely persistent (stable) radical ($Y^{\bullet}$).[11]

Remote intramolecular free radical functionalizations[16] are both beautiful and useful. They are not confined to rigid molecules (such as steroids) nor are they confined to alkoxyl radicals as the intramolecular H-atom abstracting agent. For example, nitrogen radical cations serve the same role in the Hofmann–Löffler–Freytag reaction, a simple procedure for the conversion of acyclic *N*-chloramines to substituted pyrrolidines (provided the substrate can survive the acidic conditions normally employed).[17]

Intramolecular translocations of a radical center to carbon *via* a 6-center cyclic transition state (*i.e.*, a 1,5-H-atom shift) are remarkably common in radical chemistry. Alkoxyl radicals are particularly useful for such isomerizations, not only because of their high H-atom abstracting reactivity but also because they can be generated from a wide variety of precursors (*e.g.*, nitrites, hypochlorites, hypoiodites, hydroperoxides) under mild conditions.[16] The source of the alkoxyl radical has, of course, little or no effect on product yields since these depend upon the *subsequent* chemistry of the alkoxyl radical. However, alkoxyl radical reactions can exhibit large KSEs, as first reported by Walling and coworkers.[18,19] For example,[19] *tert*-butoxyl radicals generated by the thermal decomposition of *tert*-butyl peroxalate at 40 °C in solvents containing 0.1 M cyclohexane yielded solvent-dependent *tert*-butanol/acetone ratios as shown in Scheme 2. It was hypothesized that: "Solvent interaction with the transition state for β-scission presents no difficulties, but in the transition state involving an alkoxy(l) radical and a substrate such as cyclohexene, solvent molecules should be sterically excluded from close vicinity to the alkoxy(l) radical".[18] Accordingly, Walling and Wagner[19] ascribed, "the large solvent effects on (k_H/k_β) ratios chiefly to solvation of the transition state for the β-scission process".

The correctness of Walling and Wagner's conclusion was only proven some 30 years later when rate constants for H-atom abstraction from cyclohexane by the $PhCMe_2O^{\bullet}$ radical were directly measured and shown to be invariant in CCl_4, PhH, PhCl, Me_3COH, MeCN, and acetic acid.[20] Thus, it is in the chemistry that occurs *after* formation of the alkoxyl radical that solvent effects become important and good yields of the desired product will only be obtained following a judicious choice of solvent. Indeed, many reported alkoxyl radical-mediated remote functionalizations would have failed if the substrate had been soluble only in alcohol or water. This is because H-atom abstractions from carbon by alkoxyl radicals have little or no KSE,[20] whereas three potentially

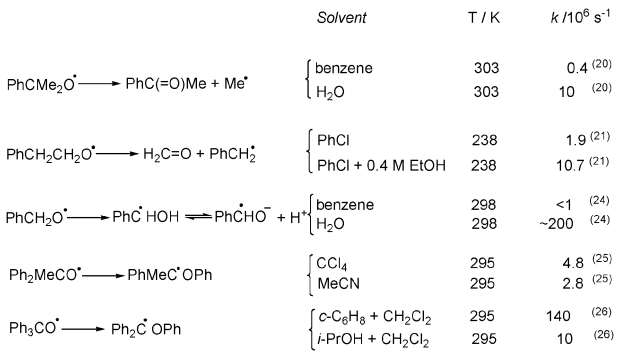


Solvent	$[Me_3COH] / [Me_2C=O]$
$CFCl_2CF_2Cl$	7.5
benzene	3.5
PhCl	2.9
MeCN	1.6
MeC(=O)OH	1.1

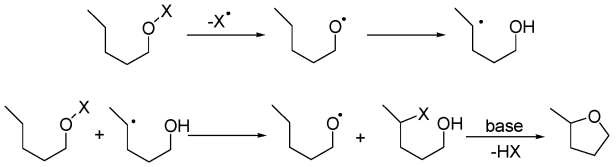
Scheme 2 *Tert*-butyl alcohol/acetone ratios for *tert*-butoxyl reactions in various solvents containing 0.1 M cyclohexane.[19]

A. L. J. Beckwith and K. U. Ingold

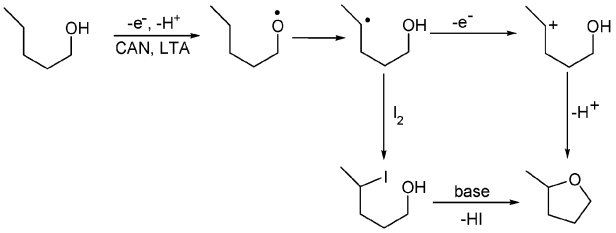
Athel Beckwith was tragically killed in a car accident on 15 May, 2010, in Canberra, Australia. He had been born in 1930 in Perth, West Australia, obtained a BSc (Hon) from the University of Western Australia in 1953 and a DPhil from Oxford in 1956. He joined the University of Adelaide in 1958 and subsequently moved to the Research School of Chemistry, Australian National University, in 1981. His honours include election as a Fellow of the Australian Academy of Science and as a Fellow of the Royal Society. He was highly respected as a thoughtful and innovative scientist, distinguished for his pioneering work in free radical chemistry. He was a kind, warm, and much loved friend and colleague. He is greatly missed.
Keith Ingold was born in 1929 in Leeds, England. He obtained his BSc (Hon. Chem.) from University College London in 1949 and a DPhil from Oxford in 1951, emigrating to Canada that same year. After 4 years of Post-Doctoral work, he joined the staff of the National Research Council from which he retired (sort of) on his 81st birthday.



Scheme 3 KSEs for some unimolecular alkoxyl radical reactions. References are placed in parentheses.



Scheme 4 Formation of halogenated alcohols and tetrahydrofurans from alkoxyl radicals (X = Cl, Br, I).



Scheme 5 One electron oxidation of pentan-1-ol to 1-methyltetrahydrofuran.

competing, unimolecular alkoxyl radical-destroying reactions have very large KSEs. Two of these unimolecular reactions have very much higher rates in water and alcohols than in non-polar solvents, while the third has lower rates in polar and H-bond donor (HBD) solvents than in non-polar solvents. These competing reactions are: (i) β-scission of the alkoxyl radical, XCR,R′O•, with formation of the carbonyl compound, R,R′C=O;[20,21] (ii) primary (and secondary) alkoxyls can form ketyl radical anions (or ketyl radicals at low pH) *via* a 1,2-H-atom shift;[22–24] and (iii) isomerization involving a 1,2-shift of an aryl group from carbon to the O• oxygen (*i.e.*, an *O*-neophyl rearrangement),[25,26] see Scheme 3.

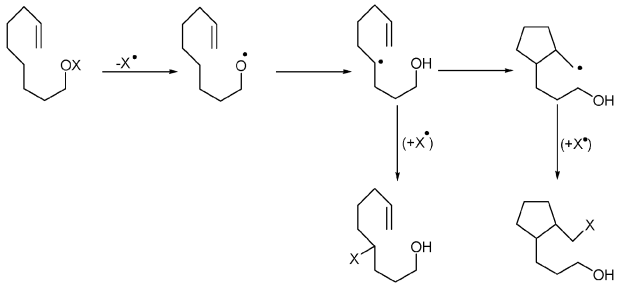
As illustrated by the kinetic data given in Scheme 3 both β-scissions and 1,2-H shifts in alkoxyl radicals are very strongly accelerated by hydroxylic solvents compared with their rates in benzene or chlorobenzene. In any particular solvent, both β-scissions and 1,2-H-atom shifts increase in rate as the product radical becomes more stable. For example, for the β-scission: PhC(O•)MeR → PhC(=O)Me + R•; the rates of loss of R• increase along the series: R = Me•, Et•, *i*-Pr•, *t*-Bu•, $PhCH_2$•, while the estimated rate constant for the 1,2-H-atom-shift for $CH_3CH_2CH_2O$• in water is only $\sim 5 \times 10^6$ s^{-1},[24] *vs.* $\sim 2 \times 10^8$ for $PhCH_2O$•.[24] The solvent-induced acceleration of β-scission is due to stronger solvation of the carbonyl product than of its precursor alkoxyl radical, particularly by HBD solvents. In sharp contrast, the *O*-neophyl rearrangements of alkoxyl radicals (1,2-aryl group shifts) are retarded by polar,[25] and particularly by HBD,[26] solvents because, for these unimolecular alkoxyl radical reactions it is the starting alkoxyl that is more strongly solvated than the product phenoxymethyl radical.

Hypohalites can provide an excellent starting point for the synthesis of tetrahydrofurans (THFs). Radical translocation in the hypohalite-derived alkoxyl radical yields 4-haloalcohols *via* a two step *chain* reaction (Scheme 4). The addition of base leads to HX elimination and cyclization.

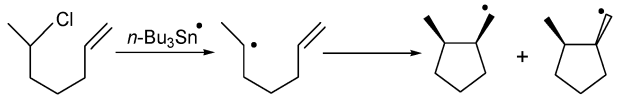
THFs can also be produced from alcohols such as 1-pentanol by very strong 1-electron oxidants, including ceric ammonium nitrate (CAN) and lead tetra-acetate (LTA).[16] In simple alcohol + oxidant systems, THF yields are poor (~20%) even with the high concentrations of the oxidant required to oxidize the carbon-centered radical to the carbocation, Scheme 5, before it undergoes some other, more typical, radical reaction. The low yields of the THFs are due, in part, to proton elimination from both the γ and ε carbon atoms of the carbocation with the formation of acyclic unsaturated alcohols.[27] CAN requires that the solvent be water (or some aqueous organic solvent mixture). For the reasons outlined above, aqueous solvents are undoubtedly the worst media to use for a desired H-atom abstraction reactions (intra- or inter-molecular) by the vast majority of alkoxyl radicals. However, with LTA as the oxidant, THF yields can be increased to 75% and more by the addition of molecular iodine.[16] The iodine traps the carbon-centered radicals at rates close to diffusion control. Elimination of HI then leads directly to the desired THF product (Scheme 5).

Since the lifetimes of most alkoxyl radicals are reduced in polar solvents, and particularly in HBD solvents, such solvents should be avoided in alkoxyl radical-based syntheses *except* in those cases where a fast β-scission or 1,2-H-atom-shift is desired. For example, the water-induced 1,2-H-atom-shift alkoxyl chemistry has been exploited[28] to produce the superoxide radical anion, the major free radical formed *in vivo*, at a known and reproducible rate for biochemical kinetic studies under physiological conditions (37 °C, pH 7).

Intramolecular H-atom abstractions by alkoxyl radicals from unactivated CH groups have also been employed to construct C–C bonds, see *e.g.*,[29] Scheme 6, which would make the yields of these cyclizations subject to KSEs. Although the configuration of the cyclopentane ring products were not reported,[29] the stereoelectronic rules governing such cyclizations have been thoroughly explored by one of us using relatively simple carbon-centered radicals generated from alkenyl halides in radical chain reactions with tin hydride[30,31] (see below). In the absence of very bulky groups, these radicals cyclize *via* a chair-like transition state that strongly favors 5-membered ring formation over the thermodynamically more stable 6-membered rings. However, there is only a rather modest control of the cyclopentane stereoselectivity, for example,[31] the hept-6-en-2-yl radical gave 1,2-dimethylcyclopentanes (*cis*/*trans* = 2.3) with only a trace of methylcyclohexane, see Scheme 7. Predominantly *cis*-substituted cyclopentanes are therefore predicted for the products of Scheme 6. It should



Scheme 6 A C–C bond-forming reaction that would be subject to significant KSEs in polar and H-bond donor solvents; X = NO, *hν* in benzene, cyclopentane yield 32%, this is a non-chain reaction; X = Cl, Fe(II) in CCl_4, cyclopentane yield 25%, this is a chain reaction (see ref. 29).



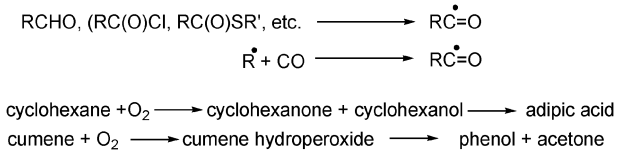
Scheme 7 Major radical products from the cyclization of the hept-6-en-2-yl radical.[31]

be noted that the intramolecular addition of carbon-centered radicals to C=C double bonds has proven to be extremely useful when constructing quaternary carbon atoms in highly congested molecules.

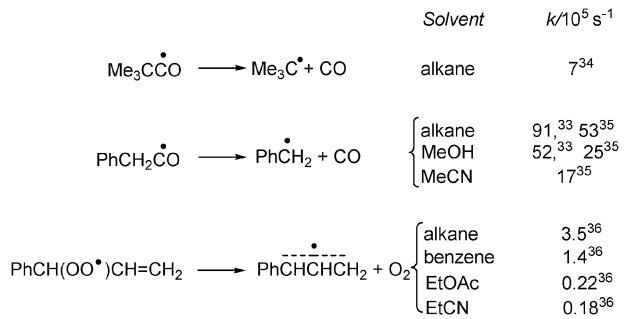
Contrasting effect of solvent polarities on the scission reactions of alkoxyl, acyl, and peroxyl radicals

The synthetic potentials of acyl radicals are well recognized.[32] These radicals may be generated from a number of molecular precursors, or from alkyl radicals under 70–90 atm of CO,[32] Scheme 8. The synthetic potential of peroxyl radicals, ROO•, is attested to by several industrially important hydrocarbon autoxidations, two of which are indicated in Scheme 8.

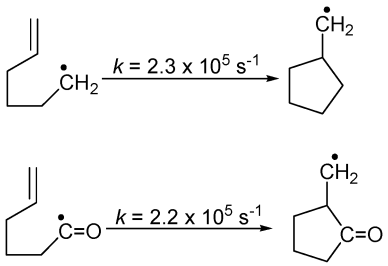
KSEs arise, of course, because of differential solvation between the reactants and transition states. Acyl and peroxyl radicals have much larger dipole moments and are stronger HB acceptors (HBAs) than the alkyl radicals formed by their unimolecular scission reactions. The transition states for both of these scission reactions will, therefore, be less strongly solvated than the starting radicals. This contrasts with the situation for alkoxyl radicals where the transition states for β-scission to carbonyl products are more strongly solvated than the starting radicals. Therefore, and in contrast to alkoxyl radicals, rate constants for the α-scission of acyl radicals[33–36] and for the β-scission of peroxyl radicals[36,37] are smaller in polar and HBD solvents than in alkanes, see Scheme 9.



Scheme 8 Syntheses of acyl radicals and two industrially important reactions of peroxyl radicals.



Scheme 9 KSEs for some unimolecular radical scission reactions at ~ 298 K.



Scheme 10 296 K cyclization kinetics for the hex-5-enyl and hex-5-enoyl radicals.[39]

The KSEs for the unimolecular scissions shown in Scheme 9 are smaller for acyl radicals than for peroxyl radicals. However, even in syntheses with acyl radicals, the carbonyl product yields at any particular CO pressure might well benefit from the use of an alcohol as the solvent, particularly in those cases where decarbonylation yields a tertiary alkyl or a resonance-stabilized carbon-centered radical and is therefore expected to be a fast reaction. We suggest that the strong HBD solvent, hexafluoro-2-propanol, $(CF_3)_2CHOH$, might prove useful for the cyclizations of such acyl radicals. Interestingly, the structurally related alcohol, $Ph(CF_3)_2COH$, has been demonstrated to form a HB-complex with a peroxyl radical that does not undergo β-scission at ambient temperatures, $Me_3CCH(OO^•)Me$.[38] As the concentration of $Ph(CF_3)_2COH$ was increased, the rate constant for the bimolecular self-reaction of these peroxyls decreased very substantially.[38] This solvent-induced increase in the persistence[11] of a peroxyl radical would, presumably, also decrease its ability to react with other molecules (by, for example, H-atom abstraction).

It is noteworthy that primary acyl radicals cyclize onto double bonds with the same rate constant as structurally comparable primary alkyl radicals,[39] see Scheme 10. This should facilitate synthetic planning.

Improving syntheses based on radical chain reactions

(i) General considerations

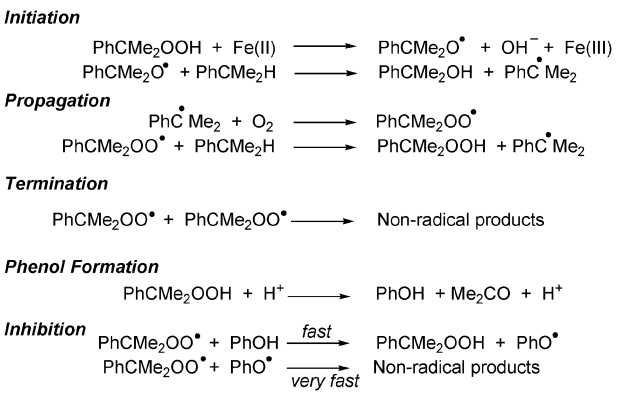
Free radical chain reactions are extremely useful in organic syntheses; witness the industrial importance of vinyl polymerizations and the two hydrocarbon oxidations indicated in Scheme 8. High yields and clean reactions require that the individual chain propagating steps be rapid. This ensures that

the radical concentration is minimized which, in turn, minimizes debilitating radical–radical chain terminating reactions so that the resulting processes are fast and have very long chain lengths (ν). In such systems, many molecules of product will be formed in each chain, while each chain requires only one initiating radical, $\mathbf{i}^{\bullet}$. The latter are commonly generated by the thermal- or photo-decomposition of azo compounds (*e.g.*, azo-*bis*-isobutyronitrile, AIBN), peroxides, or by redox chemistry, often involving hydroperoxides. The compounds synthesized in long chain reactions dominate the final product mix and the small quantities of chain termination products and initiator-derived materials can often be ignored.

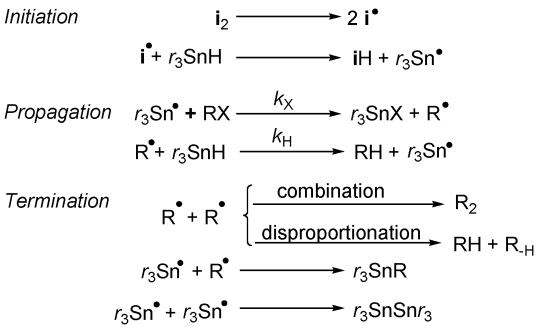
The "Achilles heel" of product formation *via* a long chain length process is the susceptibility of such chains to breakage with a consequent decrease, often dramatic, in the rate (and yield) of product formation. Chain breaking compounds are referred to as *inhibitors* if they essentially stop the reaction, and as *retarders* if they only slow the rate of the reaction. Such compounds may be present as impurities in the reagents or solvents, or may be formed (inadvertently) in the reaction, or may even be certain (apparently innocuous) solvents. An industrially important example of the inadvertent formation of an inhibitor which stops product formation in an otherwise long chain process is occasionally observed during the commercial aerial oxidation of cumene (Scheme 8). These inhibitors are Lewis acids formed, for example, by the oxidation of organosulfur-containing impurities to sulfonic acids, *etc*. In industrial practice, a weak base is often added to the reactor containing the cumene to ensure such inhibition catastrophes do not occur. The normal, uninhibited autoxidation of cumene and its potential inhibition by the phenol produced if there is an acid catalyzed decomposition of cumene hydroperoxide are shown in Scheme 11.

(ii) Tin hydride reductions[40,41]

The reduction of organic halides, RX, by organotin hydrides, r_3SnH, was recognized to occur by a chain reaction roughly fifty years ago.[42–44] The mechanism was formulated more or less as shown in Scheme 12.[44] In this early work, the reactions were generally carried out in neat halide with 1.5 mole % AIBN, though it was noted that the reduction of chlorobenzene



Scheme 11 Mechanism of cumene autoxidation initiated by Fe(II) and mechanism of its inhibition by phenol that can be formed from its hydroperoxide by Lewis acid catalysts.

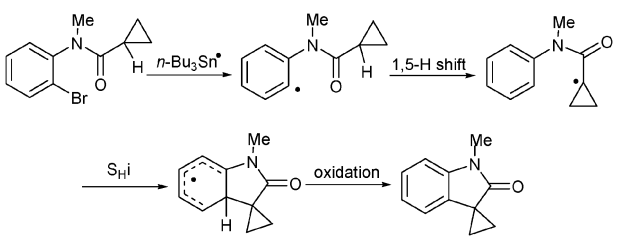


Scheme 12 Chain reaction between an organic halide, RX (X = Cl, Br, I) and an organotin hydride, r_3SnH (*r* = *n*-Bu or Ph generally), initiator, $\mathbf{i}_2$ = $[Me_2C(CN)N{=}]_2$, AIBN.

required "massive amounts" of AIBN (16 mole %)[43] which implies either a very short chain, or even a radical reaction that is not a chain process (*i.e.*, $\nu \approx 1.0$).

The elegant chemistry shown in Scheme 12 allows a carbon radical center to be generated at specific sites in organic molecules wherever a halogen atom can be introduced. This is of enormous value for radical-based organic syntheses *provided* the initial carbon-centered radical undergoes a *useful* reaction, generally C–C bond formation, before it is "wasted" by reduction by r_3SnH. Such C–C bond forming reactions will clearly be favored over reduction by low r_3SnH concentrations, a fact that has led synthetic chemists to adopt slow additions of the tin hydride to solutions containing the halide using mechanically driven hypodermic syringes (syringe pump addition). "Useful" C–C bond formation commonly involves intramolecular addition of the initial carbon radical to an unsaturated site in the starting halide (see *e.g.*, Scheme 7). Alternatively, when the halide yields a highly reactive carbon-centered radical, such as an aryl radical, intramolecular H-atom abstraction can occur even from unactivated C–H bonds (radical translocation). The new radical center can then generate the desired C–C bond by effecting an intramolecular homolytic aromatic substitution[45] and cyclizing onto the aromatic ring, see *e.g.*, Scheme 13.[46]

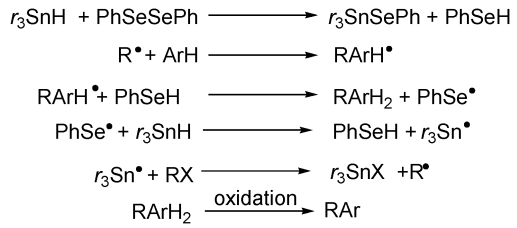
The observation that tin hydride reductions of alkyl halides were retarded by unsaturated compounds was made during the first kinetic experiments designed to measure the absolute (as opposed to the relative) rate constants for chain propagation



Scheme 13 A tin hydride mediated, non-chain, synthesis involving an intramolecular H-atom abstraction followed by an intramolecular homolytic substitution reaction (S_Hi) with cyclization to give a cyclohexadienyl radical which is oxidized to the aromatic product: *n*-Bu_3SnH (1.1 equiv.), AIBN (1.2 equiv.), toluene, 4 h, reflux (72% yield).[46]

and termination.[47] In these experiments, the rates of chain initiation were held constant at known and controlled values and overall rates of reduction of alkyl halides in cyclohexane were reproducible.[47] Small traces of olefins present in some of the alkyl halides (presumably formed by HX elimination from the halide) greatly retarded the overall reaction rate. Even with a tertiary alkyl halide, overall reaction rates were reduced by olefin addition to a reaction already underway. For example, 0.1 M cyclohexene reduced the rate of the *tert*-butyl bromide (2.8 M) + tributyltin hydride (0.12 M) reaction in cyclohexane at 25 °C by 97%.[47] However, cyclohexene did not give well-defined induction periods, meaning that it functions as a retarder rather than as an inhibitor of this chain reaction.[47] (In contrast, the stable radical, galvinoxyl, is a true inhibitor because it gave well defined induction periods.)[47] In this connection, it is worth noting that when the chains are terminated by the bimolecular self-reactions of the alkyl radicals (Scheme 12), as is the case for alkyl bromides and iodides,[47] olefin (R_{-H}) will be produced. The reaction rate will therefore decrease with time to a greater extent than can be accounted for by reagent consumption. The importance of radical–radical disproportionation relative to combination increases substantially on going from primary, through secondary, to tertiary alkyl radicals.

In the absolute kinetic experiments,[47] the solvent was deliberately chosen to be a saturated hydrocarbon rather than the benzene that had been (and still is) commonly employed in tin hydride chemistry. This was because Szwarc and coworkers[48,49] had demonstrated some years earlier that methyl radicals add quite readily to aromatics, including benzene. (Forty years after Szwarc's pioneering studies, methyl radical addition to benzene was shown to have $k = 46\ M^{-1}s^{-1}$ at 297 K).[50] While primary alkyl radicals were expected to add to benzene more slowly than methyl radicals, it nevertheless seemed prudent to avoid benzene as the solvent for the kinetic studies. This prudence turned out to have been fully justified because subsequent synthetic work (largely involving intramolecular radical additions to aromatic rings with the consequent formation of cyclohexadienyl radicals, see, *e.g.*, Scheme 13) revealed that cyclohexadienyl radicals were virtually incapable of abstracting the H-atom from tin hydrides.[51,52] The reason for this is that H-atom abstraction from r_3SnH {$D[r_3Sn\text{-}H] \approx 74$ kcal mol^{-1}} by cyclohexadienyl radicals are probably slightly endothermic with an estimated[53] rate constant not larger than 30 $M^{-1}s^{-1}$, which is too small to keep a radical chain going. In contrast, H-atom abstractions from r_3SnH by alkyl radicals are strongly exothermic and fast ($k \approx 2\text{–}10 \times 10^6\ M^{-1}\ s^{-1}$).[47,54] What all this means is that *in tin hydride-mediated reactions the addition of a radical to an aromatic ring will terminate the chain*. Therefore, syntheses in which cyclohexadienyl radicals are necessary intermediates (such as that shown in Scheme 13) will not be chain reactions, unless some very *clever* chemistry intervenes. Examples of such clever interventions include the addition of catalytic quantities of benzeneselenol (added as diphenyl diselenide, see Scheme 14)[52] or carrying out the reaction in the presence of oxygen.[55] The cyclohexadienyl radicals formed in intramolecular aromatic substitutions such as that shown in Scheme 13 are generally aromatized



Scheme 14 Homolytic aromatic substitution by a highly reactive radical, R, using a benzeneselenol-catalyzed, tin hydride chain reaction.

during the synthesis. With non-azo initiators, the aromatizing oxidation agent is probably an initiator radical.[46] However, with an azo compound, such as AIBN, as the initiator, it is the azo compound that serves this function.[46,51,52,56] As a consequence, relatively large quantities of the azo initiator are required and it "should be regarded as an expendable reagent."[46]

Turning now to the use of benzene as a solvent in tin hydride reductions, it has been reported[46] that the AIBN initiated reaction of 1-bromooctane with $(n\text{-Bu})_3SnH$ for 40 min at 70 °C yields 80% octane in cyclohexane, but yields only 28% octane in benzene. More dramatically, the reduction of methyl *p*-bromobenzoate after 2 hours yielded 97% methyl benzoate in cyclohexane but only yields 6.5% of this ester in benzene.[46] It is clear that tin hydride reductions involving primary alkyl radicals are somewhat less efficient in benzene than they would be in alkane or ester (*e.g.*, *t*-butyl acetate) solvents. Benzene is even more strongly counter-indicated as the solvent to be used in syntheses involving radicals that are even more reactive than primary alkyls, *viz*. cyclopropyl, vinyl, and aryl, if such syntheses are to be efficient.

Folklore *versus* facts

Many synthetic chemists appear to believe that solvent effects are non-existent in radical-based syntheses and can therefore be safely ignored. This view has become organic chemistry folklore but it is not supported by the facts, some of which have been presented in this tutorial review. In this review, we focused primarily on the influence of solvents on the efficiencies of remote radical functionalizations (radical translocations) and on the abilities of some solvents to convert the usual chain reaction between triorganotin hydrides and organic halides into non-chain processes. A second tutorial review is planned that will deal primarily with the effects of hydrogen bond formation on reaction rates. These can be dramatic, for example, at ambient temperatures the rate constant for abstraction of the phenolic H-atom from phenol by *any* radical will decrease by a factor of about 100,000 on changing the solvent from an alkane to hexamethylphosphorustriamide.[57] Such huge KSEs are clearly relevant in, for example, the inhibition of hydrocarbon autoxidations by phenols (Scheme 11) because they explain why phenols become useless as oxidation inhibitors in strong HBA solvents. Moreover, they suggest that HBA solvents might occasionally be useful as "protecting agents" in radical syntheses, a possibility that has not, to our knowledge, even been explored.

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