

SINGLE ELECTRON TRANSFER IN REACTIONS
INVOLVING ALKYL HALIDES AND ESTERS WITH NUCLEOPHILES

A THESIS

Presented to

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By

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SUMMARY

A variety of organic substrates possessing low reduction potentials and producing stable radical intermediates by one electron reduction have been utilized in order to evaluate the one electron transfer abilities of lithium thiolates. Thus, direct spectroscopic detection of radical intermediates was made for reactions of lithium thiolates with diaryl ketones, polynuclear hydrocarbons, trityl halides and 9-bromofluorene.

A mechanistic study for the reaction of lithium thiolates with trityl halides was conducted in more detail by (1) carrying out a complete identification of products, (2) studying the effect of the radical trap, DCPH, on product distribution, and (3) studying the effects of light and the presence of p-DNB on the reaction rate. Thus, reactions of lithium alkanethiolates with trityl halides produced α -substitution product (Ph_3CSR), and p-substitution product ($\text{p-RSC}_6\text{H}_4\text{CHPh}_2$), as well as radical by-products such as reduction product (Ph_3CH), dimerization product of trityl radicals ($\text{p-Ph}_3\text{CC}_6\text{H}_4\text{CHPh}_2$), and dimerization product of thiyl radicals (RSSR), which suggests the occurrence of SET as a predominant pathway. The presence of DCPH in the reaction of alkanethiolate with trityl halide diverted the α -substitution product as well as radical by-products to formation of the reduction product (Ph_3CH), suggesting α -substitution product as a result of non-geminate coupling of trityl and thiyl radicals. Carrying out the reaction of lithium 2-propanethiolate with trityl bromide in THF in the presence of light or absence of light or the presence of p-DNB did not affect the rate of reaction thus suggesting

the unlikelihood of a radical-radical anion chain process.

Studies of the reaction of lithium thiolates with the cyclizable alkyl iodide probe, 2,2-dimethyl-1-iodo-5-hexene yielded straight chain substitution products quantitatively. However the same reactions in the présence of the radical trap, DCPH, yielded up to 30% hydrocarbon products, suggesting a significant contribution of radicals and hence a SET pathway to describe this nucleophilic substitution reaction. For the reaction of lithium thiolates with cyclizable alkyl bromide and tosylate probes, no evidence supporting SET pathway was observed.

In the Claisen Condensation, reaction of the lithium enolate of pinacolone with ethyl p-nitrobenzoate, a paramagnetic intermediate was detected by epr spectroscopy. The concentration of a paramagnetic radical species generated in the reaction was shown to decrease in a first order fashion with a similar rate constant compared to the first order rate constant describing the rate of formation of condensation product. It was also found that the rate of disappearance of the reactant, ethyl p-nitrobenzoate, was similar to the rate of appearance of the paramagnetic intermediate under the pseudo-first order conditions.

Thus, it has been demonstrated that the reaction of p-nitrobenzoate esters with the lithium enolate of pinacolone takes place mainly via a SET pathway. However, attempts to detect the involvement of SET in reactions involving other aromatic esters using the same methods as above were largely unsuccessful.

The paramagnetic intermediate in the Saponification reaction of ethyl p-nitrobenzoate with NaOH in anhydrous solvent systems, such as THF-HMPA (9:1) and EtOH-HMPA (1:4), was detected by epr spectroscopy.

In the reaction carried out in EtOH-HMPA (1:4) homogeneously, the concentration of the paramagnetic intermediate was shown to decrease in a first order fashion with a similar rate constant to the first order rate constant of the formation of the saponification product. Thus, it has been demonstrated that the saponification reaction of ethyl p-nitrobenzoate by NaOH in EtOH-HMPA (1:4) takes place mainly via a SET pathway. An attempt to detect the paramagnetic intermediate in the reactions of methyl p-trifluoromethyl benzoate and methyl p-chlorobenzoate with NaOH was not successful.

ORGANIC REACTIONS INVOLVING ELECTRON TRANSFER

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SUMMARY

A series of experiments designed to demonstrate the occurrence of radical intermediates in an electron transfer pathway for a variety of reactions have been conducted. The experimental methods employed include product studies of reactions of compounds containing structures which can undergo a characteristic radical rearrangement (such as the conversion of 5-hexen-1-yl to cyclopentylmethyl radical), stereochemical studies, direct observation of stable radical intermediates by electron paramagnetic resonance studies and radical trapping experiments.

The cleavage of Grignard reagents designed to demonstrate the occurrence of electron transfer via a radical rearrangement has been examined with two types of electrophiles, biaryl ketones and molecular halogens. In the former case, the diagnostic cyclization was observed, which is an indication that electron transfer is a feature of the reaction pathway in the addition of Grignard reagents to biaryl ketones. In the latter case, no diagnostic rearrangements were observed, which indicates that no radical species are formed on the reaction pathway which have lifetimes sufficient for rearrangements to occur.

A variety of methods have been utilized in order to evaluate the occurrence of an electron transfer pathway for the reduction of organic halides by main-group metal hydrides. Thus, direct spectroscopic observation of a radical intermediate was made in the reduction of trityl bromide by LiAlH_4 . The reductions of a series of alkyl halides containing cyclizable radical probes were also examined and electron transfer was

found to be the predominant pathway for reactions of various hydride reagents with 6-iodo-1-heptene and with 2,2-dimethyl-1-iodo-5-hexene, since cyclized hydrocarbons were major products in these reactions. Additional evidence indicative of radical intermediates in these reductions were obtained from reactions of the iodo compounds with LiAlD_4 in the presence of the radical trap DCPH, which was shown to transfer a hydrogen atom to the radical intermediates. However, the cyclizable alkyl halide probes in which the leaving group is tosylate, chloride or bromide were reduced by metal hydrides to produce only straight-chain hydrocarbons, with the exception of 1-bromo-2,2-dimethyl-5-hexene which gave equal amounts of cyclic and straight-chain reduction products upon reaction with LiAlH_4 . Thus, the studies of the reductions of the cyclizable alkyl halide probe compounds indicate that the electron transfer pathway is much more favorable for iodo compounds as compared to compounds with other leaving groups.

The stereochemistry of the reduction of organic halides by LiAlD_4 in THF was also examined. It has been shown that (-)-1-chloro-1-phenylethane and (-)-1-bromo-1-phenylethane are reduced by LiAlD_4 with predominant inversion of configuration. Also, (-)-2-tosyloctane, (+)-2-chlorooctane and (+)-2-bromooctane are reduced by LiAlD_4 with the same stereospecificity, but (+)-2-iodooctane is reduced by LiAlD_4 with substantially less stereospecificity. Thus, these stereochemical studies also indicate that an electron transfer pathway is operative for the reduction of secondary alkyl iodides by LiAlD_4 .

The studies of the reactions of cyclizable secondary alkyl halides (6-halo-1-heptenes) with sodium trimethyltin have demonstrated the

occurrence of an electron transfer pathway, since tetraalkyltin products containing a cyclized alkyl group were formed. The extent of electron transfer was found to be a function of the leaving group and follows the trend $I > Br > Cl$ and no electron transfer was observed for the OTs leaving group. The radical trapping agent DCPH was found to be very effective in trapping the radical intermediate to form the hydrocarbon product instead of the tetraalkyltin product. Also, it was shown that the reaction of sodium trimethyltin with the 2-halo-octanes proceeds with predominant inversion of configuration. Thus, it has been shown that the reaction of sodium trimethyltin with secondary alkyl halides proceeds by an electron transfer pathway to form an intermediate with sufficient radical character to undergo cyclization or be trapped by DCPH, but also the intermediate is converted to tetraalkyltin product with predominant inversion of configuration.

By examining the products of reactions of cyclizable alkyl halides with various nucleophiles the possible occurrence of electron transfer pathways has been evaluated. Thus, it was shown that alkali metal alkoxides, thioalkoxides and enolates do not act as electron transfer agents toward alkyl halides, since no cyclized products were observed in these systems. However, it has been demonstrated that radical intermediates are formed in reactions of lithium alkylamides and lithium alkylcuprates with iodo compounds, since large amounts of cyclized products were formed from the cyclizable probes in these reactions.