

# EFFECT OF STRUCTURAL FEATURES OF TRI-FUNCTIONALIZED ARYL PHOSPHATE ISOMERS IN THE $S_{RN}1$ BEHAVIOUR. A DFT STUDY

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## Abstract

Under irradiation, the 1,3-bis(diethoxyphosphoryloxy)-4-chlorobenzene (**3**) and the 1,4-bis(diethoxyphosphoryloxy)-3-chlorobenzene (**4**) react with trimethyltinsodium (**1**) in liquid ammonia giving entirely different distribution of stannylated products. Evidence for the involvement of an  $S_{RN}1$  mechanism was obtained and through a theoretical DFT study we explain the differences observed between both isomers.

**Keywords:** DFT methods,  $S_{RN}1$ , Aryl Phosphate Isomers

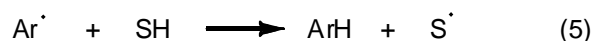
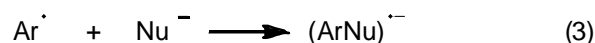
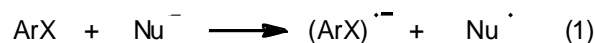
## Introduction

The preparation of organotin compounds and its application as intermediates has become a very important aspect in organic chemistry.<sup>1</sup> For example, palladium-catalyzed reactions involving aryltin compounds have found wide application in the synthesis of aromatic and heterocyclic compounds.<sup>2</sup> In connection with the synthetic importance of these reactions, our group has been involved in searching new synthetic routes to organostannanes by the  $S_{RN}1$  mechanism.<sup>3</sup>

Aromatic nucleophilic substitution via the  $S_{RN}1$  mechanism enables the substitution of appropriate nucleofuges on unactivated aromatic systems with suitable nucleophiles.<sup>4</sup> The proposed mechanism is a chain process (Scheme 1). In the initiation step there is an electron transfer (ET) from the nucleophile to the starting substrate (eq 1). If this ET is not spontaneous, it could be induced by UV light.<sup>4</sup>

The key species of the process,  $Ar\cdot$ , obtained by the reductive cleavage of  $ArX\cdot$  (eq 2), combines with the nucleophile to give  $ArNu\cdot$  (eq 3), which in turn reduces the starting aromatic substrate. The radical anion  $ArX\cdot$  is regenerated according to eq. 4. It should be noted that the coupling with the nucleophile is not the only reaction that aryl radicals can undergo: hydrogen atom transfer from the solvent is one of the most important side

reactions (eq 5). This competitive reaction is prevented by using liquid ammonia as solvent, which is a poor hydrogen atom donor.<sup>4</sup>



### Scheme 1. S<sub>RN</sub>1 Mechanism

We have demonstrated that a substrate containing three leaving groups, i.e. 1,3,5-tris(diethoxyphosphoryloxy)benzene reacts, with trimethylstannylsodium (**1**) in liquid ammonia under irradiation (6 h) to afford 1,3,5-tris(trimethylstannyl)benzene (**5**, 57%) together with traces of 1,3-bis(trimethylestannyl)benzene (**6**, ca. 1% by GC) through an S<sub>RN</sub>1 mechanism.<sup>3d</sup> As well, 1,3-bis(diethoxyphosphoryloxy)-5-chlorobenzene, under similar reaction conditions (30 min), by S<sub>RN</sub>1, yielded **5** together with **6** in a 87:13 ratio.<sup>5</sup>

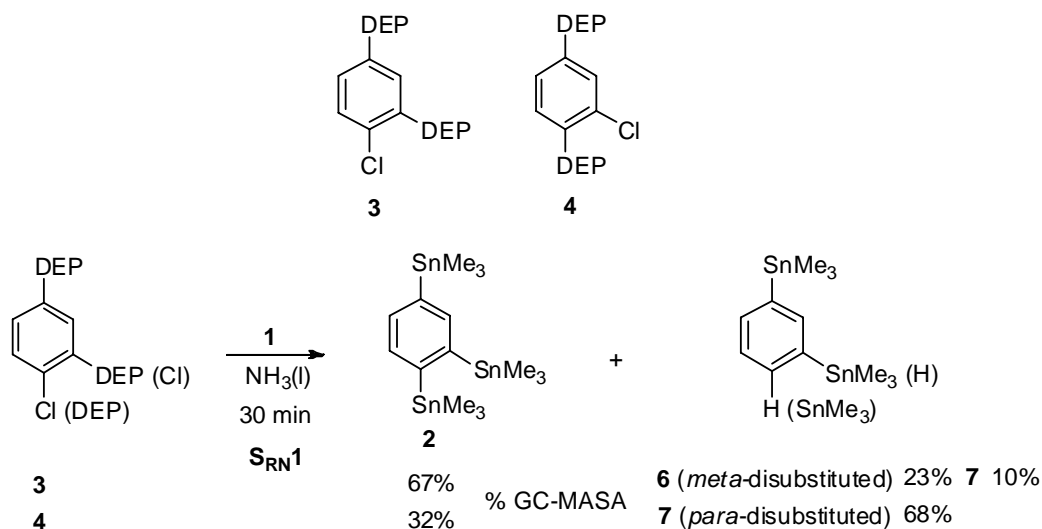
Also, Rossi *et al* have reported the synthesis of **5** by the reaction of 1,3,5-trichlorobenzene with an excess of **1** in liquid ammonia under irradiation.<sup>6</sup> So, both diethoxyphosphoryloxy (DEP) and/or chloro- trisubstituted benzenes could be excellent starting materials for the synthesis of tristannylated products by an S<sub>RN</sub>1 mechanism.

On the other hand, the results obtained in previous work where we have obtained 1,2-; 1,3- and 1,4-bis(trimethylstannyl)benzene in good to excellent yields, by S<sub>RN</sub>1, starting from DEP and/or chloro disubstituted aryl compounds,<sup>3b,3f</sup> prompted us to study the scope of S<sub>RN</sub>1 in the polystannylation with trimethylstannylsodium (**1**), in liquid ammonia as solvent, of aryl phosphates supporting three nucleofugal groups at different relative positions from the previous studies. Moreover, in order to explain the experimental results, a theoretical analysis was performed with DFT methods and the B3LYP functional.

## Results and Discussion

In order to synthesize 1,2,4-tris(trimethylstannyl)benzene (**2**) we use as starting substrates 1,3-bis(diethoxyphosphoryl)oxy-4-chlorobenzene (**3**) and 1,4-bis(diethoxyphosphoryl)oxy-3-chlorobenzene (**4**).

Irradiation (30 min) of **3** and **4** in liquid ammonia in the presence of **1** (1/3.6 ratio) led to entirely different product distributions (Scheme 2).



**Scheme 2**

Thus, the photostimulated reaction of **3** with **1** proceeds smoothly to afford **2**, **6** and 1,4-bis(trimethylestannyl)benzene (**7**) in a 67:23:10 ratio; whereas irradiation of **4**, under the same reaction conditions, yielded **2** and **7** in a 32:68 ratio.

When these reactions were carried out in the dark, we found that **4** yielded exclusively 1,4-bis(diethoxyphosphoryl)oxy-benzene (**8**) as a consequence of C-Cl bond fragmentation in the radical anion  $4^{\cdot-}$  after a thermal or spontaneous electron transfer from **1**. This reaction was partially inhibited by the addition of *p*-dinitrobenzene (*p*-DNB, 20%), a well-known inhibitor of  $S_{RN}1$  reactions. On the other hand, under these conditions, **3** afforded 1,3-bis(diethoxyphosphoryl)oxy-benzene (**9**) and substantial amounts of starting substrate. This reaction was fully inhibited by the addition of *p*-DNB (20%).

These results suggest that the cleavage of C-Cl bond occurs by a spontaneous ET for the substrate **3**, whereas **4** fragments through two different mechanisms, by ET and by an ionic process named HME (halogen-metal exchange).

Moreover, **2** and different isomers of bis(trimethylstannyl)benzene were observed when we carried out the reaction of **1** with both **3** and **4** isomers by solvated electron initiation (Na metal in liquid ammonia).

From the above mentioned results it is evident that, in the systems studied, the substitution products were formed exclusively through an  $S_{RN}1$  mechanism, a chain process in which radicals and radical anions are involved as intermediates.

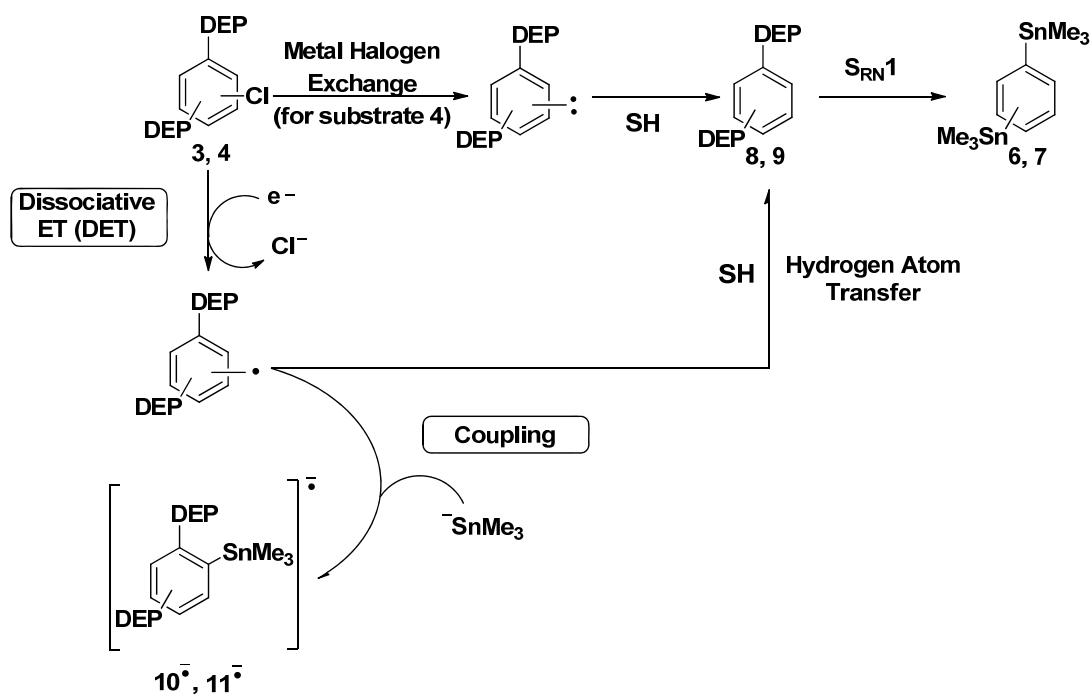
The differences in product distribution upon irradiation of compounds **3** and **4** were unexpected since the  $\pi^*$  MO energy is not likely to be affected by the relative position of the substituents in the ring; both substrates would have similar electron affinities making feasible their single-electron reduction.

In a previous theoretical study of the reactivity of 1- and 2-(diethoxyphosphoryl)oxy-1,3-cyclohexadienes towards **1** under  $S_{RN}1$  conditions,<sup>3j</sup> we have demonstrated that the spin distribution on C-*ipso* to the leaving group can be taken as an indication of a more easy dissociation for the corresponding radical anions.

In order to obtain information on this matter, we theoretically study the neutrals and the radical anions of compounds **3'** and **4'**, the dimethoxyphosphoryloxy (DMP) analogs of **3** and **4**, respectively. Calculations were performed with the B3LYP DFT functional with the LACVP pseudopotential for Sn and the 6-31+G\* basis set for C, H, O and P.

The LUMO MOs of the neutral compounds have  $\pi$  symmetry and they are, as expected, similar in energy (-0.03314 eV and -0.03726 eV for **3'** and **4'**, respectively).

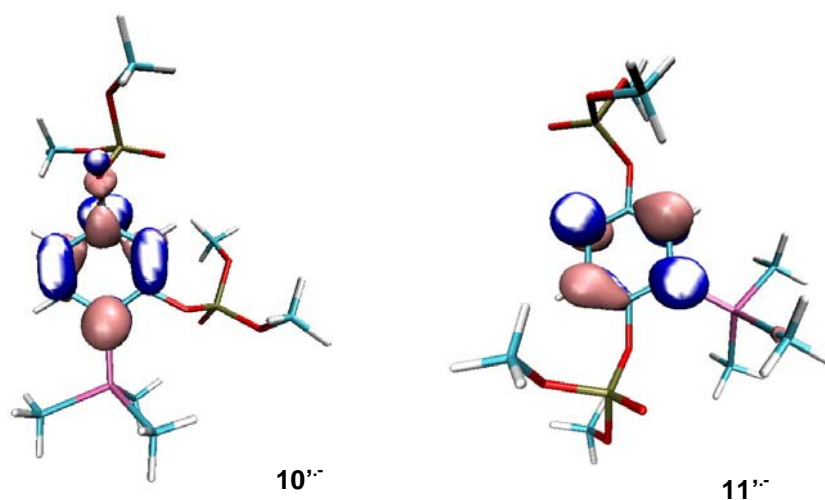
In agreement with the fact that the chloro leaving group is more reactive than DEP towards **1** in liquid ammonia,<sup>3b</sup> both substrates, **3** and **4**, after ET followed by C-Cl bond fragmentation (dissociative ET - DET) gave the intermediate radicals, which could abstract an hydrogen atom from the solvent affording **9** and **8**, correspondingly, or could couple with the trimethylstannyl anion yielding the mono substituted radical anions 1,3-bis(diethoxyphosphoryl)oxy-4-trimethylstannylbenzene (**10 $\cdot^-$** ) and 1,4-bis(diethoxyphosphoryl)oxy-3-trimethylstannylbenzene (**11 $\cdot^-$** ), respectively. On the other hand, as we mentioned earlier, the HME pathway competes efficiently with the DET process for substrate **4**, giving **8** in the course of an ionic mechanism. Through an  $S_{RN}1$  mechanism, under the reaction conditions, **8** and **9** afforded the bis(trimethylstannyl)benzene derivatives **7** and **6**, respectively (Scheme 3).



Scheme 3

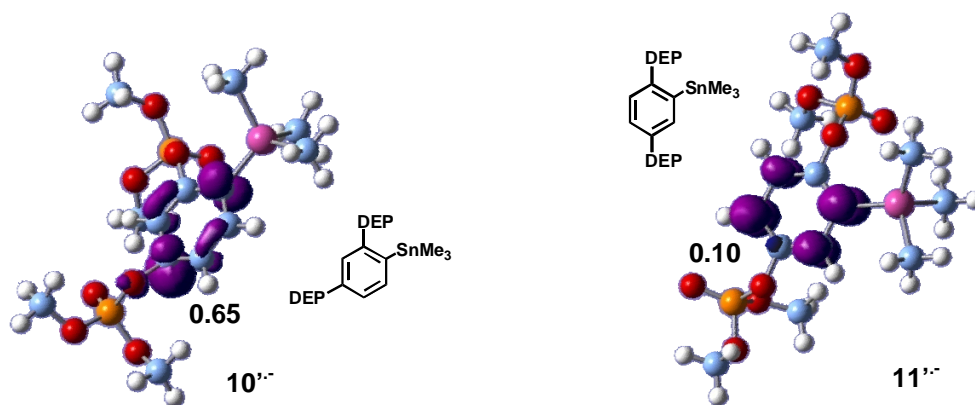
Besides the observed differences in the reactivity of substrates **3** and **4**, reactivity of **10**<sup>-</sup> and **11**<sup>-</sup> toward further substitutions through the ET process could be also responsible of the final product distribution.

At first, we considered in **10**<sup>-</sup> and **11**<sup>-</sup> the dissociation of the second leaving group DEP *para*- or *meta*- with respect to stannyl moiety. No thermodynamic differences were found for the process, being both exothermic; nevertheless, a thorough analysis of the SOMO OMs of these radical anions showed significant differences. Despite both have  $\pi$  symmetry, as can be seen in Figure 1, **11**<sup>-</sup> have a C-*ipso* node at the ortho position with respect to the stannyl moiety.



**Figure 1.** SOMO OMs of **10**<sup>\bullet-</sup> and **11**<sup>\bullet-</sup>.

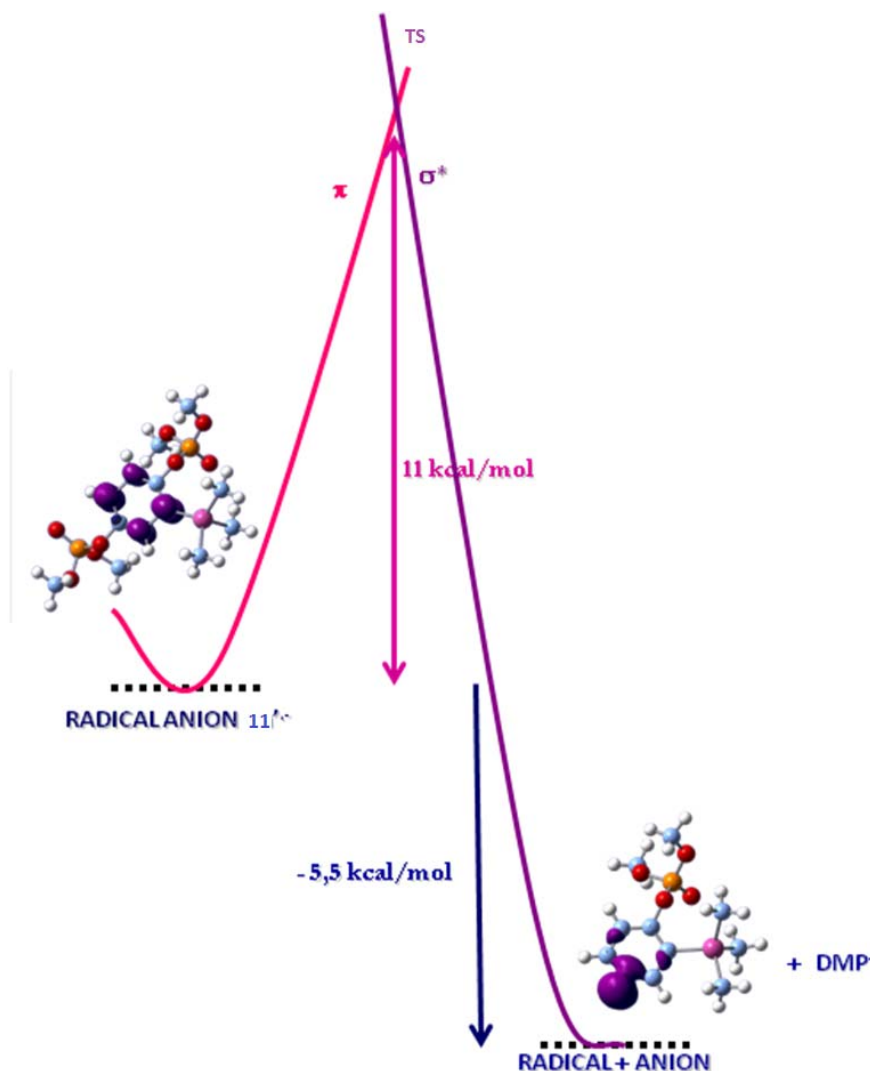
Moreover, the unpaired spin distribution at the C-*ipso* to DEP in *meta*-position respect to stannyl moiety in **11**<sup>-</sup> is considerably lower than the spin density at the C-*ipso* to DEP in *para*-position of **10**<sup>-</sup>, that is, 0.10 and 0.65 respectively (Figure 2).

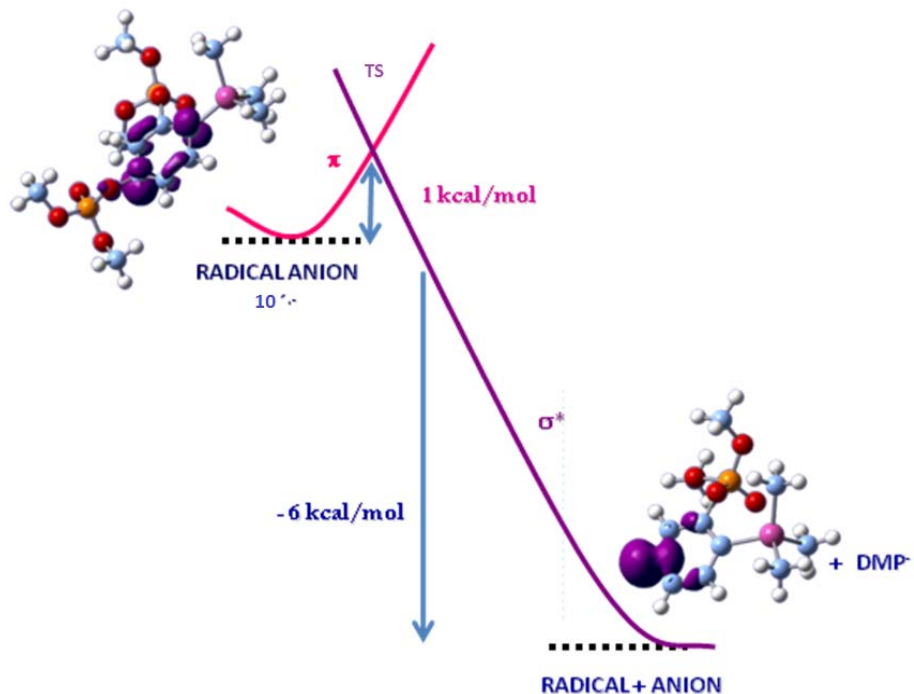


**Figure 2.** Gas phase B3LYP/6-31+G\* spin density (violet) of **10**<sup>\bullet-</sup> and **11**<sup>\bullet-</sup>.

It has been shown that the nodal properties of the MO that hosts the unpaired spin density distribution are relevant factors for the cleavage of radical anions.<sup>7</sup>

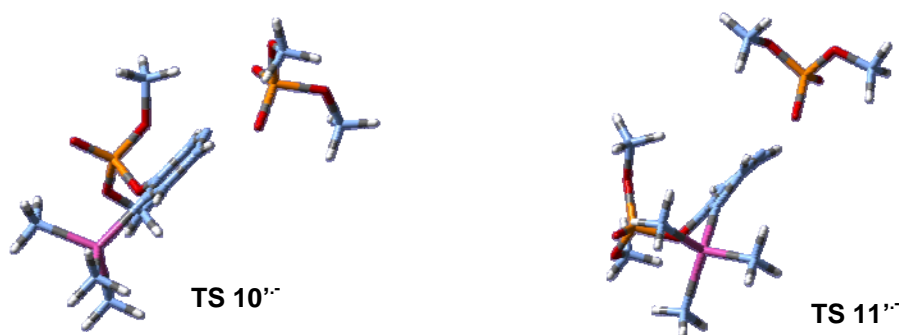
On the other hand, the systematic inspection of the potential energy surface (PES) of both radical anions for the dissociation through an intramolecular dissociative ET (intra-DET) from the  $\pi$  system to the  $\sigma^*$  C-OP bond shows as expected from the low spin density at the C-*ipso* to its leaving groups, that radical anion **11**<sup>•-</sup> dissociates at its *meta*-position with higher activation energy, 11 kcal/mol vs 1 kcal/mol for **10**<sup>•-</sup>, as can be seen from Figure 3.





**Figure 3.** PES for C-OP bond fragmentation of  $11^{\bullet-}$  and  $10^{\bullet-}$  (Spin densities are showed)

As shown in Figure 4, transition states (TS) for the dissociation of  $10^{\bullet-}$  and  $11^{\bullet-}$  are very different. Thus, the  $11^{\bullet-}$  TS loses its planarity during the fragmentation with a loss of aromaticity, what is in agreement with a higher activation barrier for the process. Probably this intra-DET is favored under irradiation.



**Figure 4.** Transition States for C-OP bond fragmentation of  $10^{\bullet-}$  and  $11^{\bullet-}$

Through a subsequent sequence of coupling with **1** - fragmentation of the second C-DEP bond and a third coupling with **1**, substrates **3** and **4** afford the radical anion **2 $^{\bullet-}$** .

We thought that these theoretical results support the experimental results. This system is an interesting example of isomers whose radical anions dissociate with similar

thermochemistry but different activation energy due to differences in their SOMOs composition.

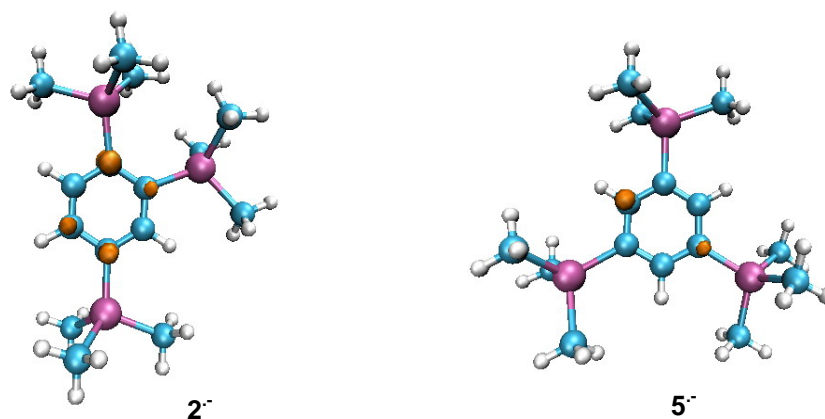
From the above mentioned results it is evident that the synthesis of product **2** appears to be dependent on some structural features of the starting substrate.

It should be noted that the undesired secondary products **6** and **7** derived from **3** and **4**, respectively, are formed by the most important side reactions in  $S_{RN}1$  process, hydrogen atom transfer to the intermediate radicals and subsequent substitution. Moreover, the HME mechanism competes efficiently with the ET process in substrate **4**, affording higher amounts of **8** (See Scheme 3). This fact together with the lower spin density at the *C-*ipso** support the experimental results: 1,4- bis(trimethylstannyl)benzene (**7**) is the main product in this reaction.

Also, it is essential to mention that  $2^{\cdot-}$  may suffer two competing reactions: ET to the starting substrate or generation of a radical (by expelling a trimethylstannyl anion) which ultimately leads to disubstitution by products by hydrogen atom transfer from the solvent.

This intra-DET cleavage responds to a radical anion process and it increases under strong electron donating conditions (Na in liquid ammonia). As can be seen from Figure 5, the fragmentation pattern is in agreement with the unpaired spin distribution calculated for  $2^{\cdot-}$ .

Although  $5^{\cdot-}$  suffers fragmentation in presence of solvated electrons, this reaction is not important and is not a competitive process. This fact is also in agreement with the distribution of spin density observed for this radical anion (Figure 5).



**Figure 5.** Gas phase B3LYP/6-31+G\*/LACVP (Sn) spin density (orange) of  $2^{\cdot-}$  and  $5^{\cdot-}$

These results are coincident with those obtained by Rossi and Chopa indicating that the most efficient tris(trimethylstannyl)benzene derivative that could be synthesized through an  $S_{RN}1$  process is the 1,3,5-tris(trimethylstannyl)benzene under appropriate experimental conditions.



## Conclusions

We informed the study of the  $S_{RN}1$  reaction between substrates **3** and **4** and **1** in liquid ammonia for the synthesis of 1,2,4-tris(trimethylstannyl)benzene (**2**) and its stability under the reaction conditions. Also, we reported another example that shows that structurally similar compounds do not behave in the same way under ET conditions and that this behavior is mainly due to differences in spin density of their radical anion intermediates.

## Experimental Section

All manipulations were performed under nitrogen. The solvents used were dried and distilled in accordance with standard procedures. Irradiation was conducted in a reactor made of Pyrex, equipped with four 250 W UV lamps emitting maximally at 350 nm (water-refrigerated). To carry out the reaction in dark, the reaction flask was wrapped with aluminium foil.

Diethyl aryl phosphates were prepared by the Kenner and Williams<sup>8</sup> method and characterized by IR and NMR spectroscopy, and used without further purification.

### *1,3-bis(diethoxyphosphoryl)oxy-4-chlorobenzene (3)*

Kenner's method was employed for the reaction of 4-chlorobenzene-1,3-diol (5.0 mmol, 0.722 g) with diethyl hydrogen phosphate (10.4 mmol, 1.340 mL) and triethylamine (10.4 mmol, 1.570 mL) in  $CCl_4$  (4 mL) as solvent. **3** was obtained as a pale yellow liquid (75%) and was used without further purification.

### *1,4-bis(diethoxyphosphoryl)oxy-3-chlorobenzene (4)*

The title compound was obtained as a pale yellow liquid (1.666 g, 4.0 mmol, 80%) and was used without further purification.

### *1,2,4-tris(trimethylstannyl)benzene (2)*

Representative Procedure for Photostimulated Reactions in Liquid Ammonia: In a 250 mL two-necked round-bottomed flask, equipped with a cold finger condenser charged with acetone-liquid nitrogen, a nitrogen inlet and magnetic stirrer were condensed 180 mL of Na-dried ammonia.  $Me_3SnCl$  (0.660 g, 3.3 mmol) was dissolved and sodium metal (0.174 g, 7.5 mmol) was added until the blue color persisted for at least 5 min. When the blue color disappeared, **3** (1.0 mmol, 0.416 g) was added dropwise and the solution was irradiated with stirring. The reaction was quenched with  $IMe$  (96  $\mu L$ , 3.3 mmol), 10 mL of  $Et_2O$  was added and then liquid ammonia was allowed to evaporate. The resultant solution was treated with water and extracted with  $Et_2O$  (3  $\times$  30 mL). The crude extract was diluted with  $Et_2O$  to a volume of 100 mL and analyzed by GC-MS.

## Computational Procedure

The calculations were performed with Gaussian03.<sup>9</sup> The initial conformational analysis of compounds was performed with the semiempirical AM1 method. The geometry of the most stable conformers thus obtained was used as starting point for the B3LYP<sup>10</sup> studies of their radical anions with the LACVP<sup>11</sup> pseudopotential for heavier elements (Sn) and the 6-31+G\* (C, H, O, P). The exploration of the potential surface was carried out varying the selected coordinate ( $C_{aromatic}-OP$  bond distance) with full optimization for the remainder degrees of freedom. The characterization of all stationary points was done by Hessian matrix calculations of geometries obtained with full optimization for a minimum and by using the TS methodology for a transition state. In all the cases, the spin contamination along the whole fragmentation paths was negligible. The zero point energy corrections were made for the thermodynamic quantities. The energies in solution were obtained with full geometry optimization within the Tomasi's polarized continuum model (PCM)<sup>12</sup> as implemented in Gaussian03. The figures were built with the GaussView program using a spin density isosurface of 0.02.

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