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Channeling the SmI_2 Reactions to the Radical Path: Radicals Resisting Reduction by SmI_2

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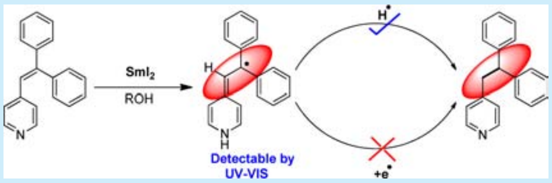
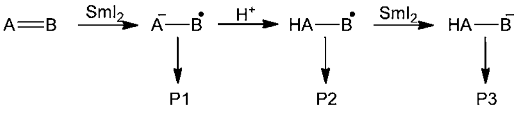
Ⓢ *Supporting Information*

ABSTRACT: Studies on the reaction of 4-(2,2-diphenylvinyl)pyridine with SmI_2 revealed that the intermediate radical strongly resists further reduction to the corresponding anion. The resistance of the radical to accepting another electron is traced to its stabilization by the nitrogen lone pair. The literature suggests that oxygen may also play a role similar to that of nitrogen in directing the course of the reaction toward radical rather than to anionic chemistry.

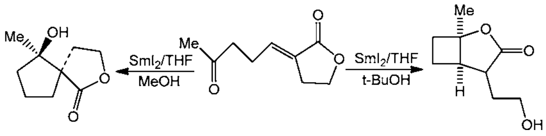


One of the major reasons for the popularity of samarium diiodide as a reducing agent[1] is its versatility. While in hydride-transfer reagents reduction of a general double bond A═B will result in an anionic intermediate HA–B⁻, reduction by SmI_2 may result in three different reactive intermediates, each of which may undergo a different inter- and intramolecular reaction leading to various products (P1–P3; Scheme 1).

Scheme 1



We have shown in the past that one can apply some control over the reaction paths by an educated choice of the proton donor in the reaction.[2] Proton donors which complex to SmI_2, such as MeOH or water, will protonate the radical anion efficiently leading to P2. That is because the protonation takes place within the ion pair in a unimolecular fashion. Therefore, the production of P1 will be largely reduced. However, when a proton donor which is incapable of forming a complex with SmI_2 is used, the radical anion will not be protonated and the formation of P1 is enabled at the expense of the production of P2 and P3. This model allows us to explain[2a] the enigma posed by the elegant work of Procter et al., who discovered that MeOH and *t*-BuOH induced different cyclization modes (eq 1).[3] It was suggested that the *t*-BuOH-derived product involves



(1)

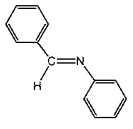
the action of the negative charge of the radical anion (P1) while the product obtained in the presence of MeOH seems to be formed by the radical path (P2).

However, arriving at the radical intermediate may lead not only to P2 but also to P3. The present paper identifies the conditions for an effective prevention of the conversion of the radical (leading to P2) into the anion (leading to P3).

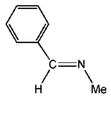
We have recently studied the reduction by SmI_2 of substrates containing nitrogen in the π system.[4,5] We suggest that using these and similar types of substrates can slow the electron transfer from SmI_2 to the radical, thereby increasing the likelihood of P2 as the dominant reaction path (Scheme 1).

The nitrogen-containing substrates BAI, BMI and BPI, studied previously by us, display a very colorful and unique behavior in their reactions with SmI_2.[4a]

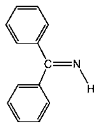
The reactions of these substrates display, among other unique features, autocatalysis and zero-order kinetics which are atypical of other substrates.



BAI



BMI



BPI

When the nitrogen atom was moved from the double bond undergoing the reduction to a remote position, yet still in conjugation with the central bond as in **4SP**, the aforementioned phenomena repeated themselves.[5] The most profound feature observed for **4SP** was the resistance of the intermediate radical to accepting another electron. Namely, even when excess SmI_2 was used, the radical dimerized as shown in eq 2 and no reduced monomer was obtained.

The limited tendency of the radical to accept an electron is surprising in light of the rate constant measured for electron transfer from SmI_2, which is $5 \times 10^5\ M^{-1}\ s^{-1}$ to alkyl radical[6] and $5.3 \times 10^7\ M^{-1}\ s^{-1}$ to benzyl radical.[7]

Following this discovery, we studied **BSP**, a derivative of **4SP** in which a hydrogen atom was replaced by a phenyl group in

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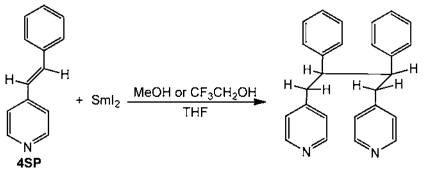
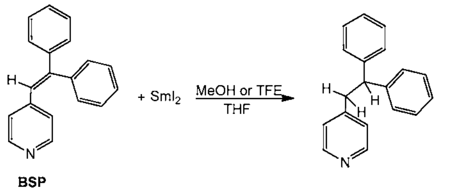


(2)

order to block the radical combination path. As will be shown below, this led to the formation of a relatively stable radical which could be observed by UV−vis spectroscopy.

As expected, the replacement of a hydrogen atom by a phenyl ring indeed quenched the dimerization process, and the only product obtained was the reduced monomer (eq 3).



(3)

However, as will be shown later on, this reduced monomer was NOT obtained via P3, but rather via the P2 path. Monitoring the kinetics of the reaction in the presence of MeOH or trifluoroethanol (TFE) at the absorption maximum of the SmI$_2$ (619 nm) under pseudo-first-order conditions showed that instead of the expected decrease in the absorption due to the disappearance of the SmI$_2$ an unexpected rapid increase of the absorption is observed. This absorption is then followed by a slow decay (Figure 1 and Figures S1, Supporting Information).

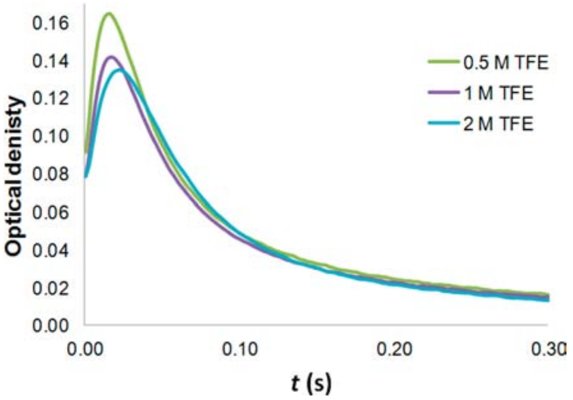
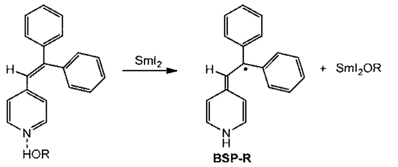


Figure 1. Absorption at 619 nm vs time for the reaction of **BSP** (5 mM) and SmI$_2$ (0.5 mM) in THF in the presence of variable amounts of TFE.

We have shown for **4SP**,[5] that in the first step, a hydrogen bond is formed between the proton donor and the lone pair on the nitrogen. In the second step, concomitant with the electron transfer, the hydrogen bond tightens to give a N−H bond, and the corresponding radical is formed. In the case of **4SP**, the radical undergoes rapid combination to give the dimer. In the present case, because the dimerization step is inhibited by the added phenyl group, the increase in the absorbance is attributed to the formation of the corresponding radical (**BSP-R**, eq 4).

Continuous monitoring of the reaction using a diode array showed that λ_{max} of the radical is around 606 nm (Figure 2).



(4)

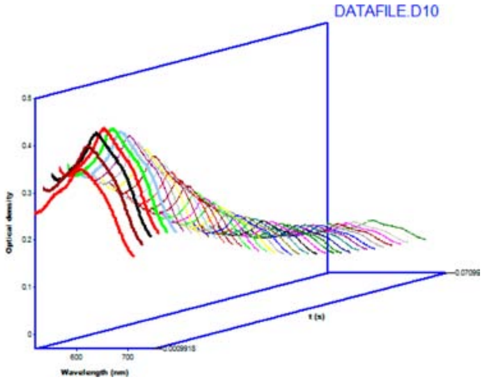


Figure 2. Diode array monitoring of the reaction of **BSP** (5 mM) and SmI$_2$ (0.5 mM) in THF in the presence of MeOH.

Ab initio calculations at the B3P86/6-311++G(d,p) and MO62*X*/6-311++G(d,p)[8] levels showed absorption maxima with varying intensities in the range 450−650 nm, in agreement with the observed absorption (see the Supporting Information). Thus, the chemical rationale, and the agreement between the spectroscopic observation and the quantum mechanical calculations, support the conclusion that the observed intermediate is indeed **BSP-R**.

One of the most important features of this radical is that the alcohol concentration has hardly any effect on the rate of its decay. This is evident from Figure 1 and is unambiguously demonstrated in the reactions where 1 and 100 mM of acetic acid were used (Figure S2, Supporting Information). Since there is no dimerization and in light of the lack of rate dependence on the proton donor type or concentration, the question is what is the mechanism of the **BSP-R** disappearance? It should be pointed out that the observed kinetic traces for the decay clearly do not follow first-order kinetics. On the other hand, starting with the analysis after ca. the first 20% of the reaction, assuming that at this point there is no additional production of the radical and the only reaction observed is the decay of the radical, the general second-order equation for $A + A \rightarrow P$ (eq S1, Supporting Information)[9] gives a good straight line for the plot of 1/O.D. vs t (Figure S3, Supporting Information).

In these plots, A was replaced by the optical density (O.D.) which is proportional to the concentration (A) of the radical. The average slope for the bimolecular reactions of **BSP-R** in the presence of MeOH (0.5−2 M), TFE (0.5−2 M), or AcOH (0.001, 0.1 M) is 231 ± 29 with $r^2 \geq 0.997$. Despite the lack of dependence of the rate of the radical disappearance on the proton donor concentration, we have studied the kinetic H/D effect using MeOH and MeOD. Surprisingly, using the MeOH/D concentrations of 0.5, 1, and 2 M, we have found an H/D isotope effect of 3.5 ± 0.3 (Figure 3 and Figure S4, Supporting Information). It should be noted the maximum absorbance in the kinetic trace is higher for MeOD than for MeOH because the competing annihilation reaction of the radical is slower.

The absence of proton donor effect on the rate, on the one hand, and the existence of a H/D isotope effect on the other,

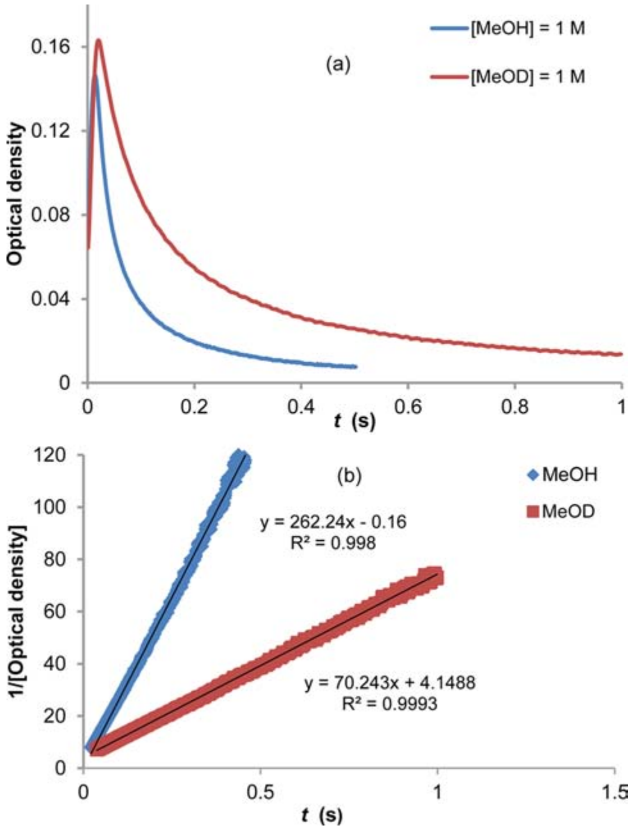
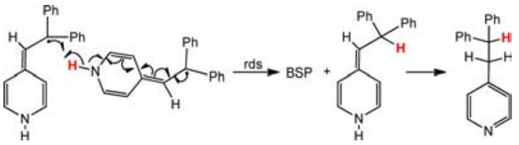


Figure 3. Kinetic isotope effect for the reaction of **BSP** (5 mM) andSmI$_2$ (0.5 mM) in THF in the presence of MeOH/D (1 M): (a) kinetic traces; (b) fit to second-order equation.

clearly point at hydrogen radical transfer as the rate-determining step. This, combined with the bimolecular nature of the reaction, leads to a mechanism in which one **BSP-R** transfers a hydrogen radical to the other (Scheme 2). The final step is prototropy with rearomatization of the pyridine ring.

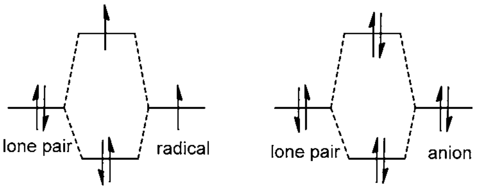
Scheme 2



A thought-provoking question is why **BSP-R** and the corresponding radical of **4SP** resist further reduction by SmI$_2$ to generate the corresponding anion. We suggest that this resistance results from the differential interaction between the nitrogen lone pair and the single electron in the radical relative to that with the two electrons in the anion.

In general, a radical interacting with a lone pair derives stability from this interaction. In the MO terminology, this stabilization stems from the fact that in the MO generated (Scheme 3), two electrons are stabilized while only one electron goes up in energy.[10] This stabilization of the radical is contrasted by a destabilization of the anion. The latter destabilization stems from the fact that the denominator of the interaction energy term is 1 ± S (where S is the overlap integral). Consequently, the antibonding orbital is destabilized slightly more than the bonding orbital is stabilized.[11] Namely, in the anion, the antibonding orbital is now doubly occupied,

Scheme 3



and since this orbital is shifted upward in energy more than the bonding orbital is shifted downward, the net outcome is the destabilization known as the 4-electron destabilization effect.

Additional support for our suggestion that the lone pair is responsible for the resistance of **BSP-R** to accept another electron comes from ab initio calculations. We have calculated at the B3LYP/6-31+G* level with the polarizable continuum model (dielectric constant of THF) the energy of both the radical and its corresponding anion. In the second step, we have rotated the pyridine ring out of plane so that its π-system will not interact with the radical/carbanion (the two conformations are shown for the radical in Figure S5, Supporting Information). This out-of-plane rotation causes an increase in energy of 12.6 kcal/mol for the radical and only 5.3 kcal/mol for the anion. Thus, the pyridine ring differential effect on the two species amounts to ca. 7 kcal/mol. This value translates to a rate retardation of ca. 6 orders of magnitude for an electron transfer to **BSP-R**.

It is also clear from Scheme 3 that electron transfer to the SOMO will be more difficult than to a radical, which does not enjoy the lone pair stabilization because of the difference in energy of the two orbitals.

In conclusion, the resistance of the radical to further reduction by SmI$_2$ is derived from the lone pair induced stabilization of the radical as well as the concomitant destabilization of the corresponding anion.

In principle, this effect can be exploited using other lone-pair-carrying atoms such as oxygen. Ab initio calculations at the B3LYP/6-31+G* level[8] on simple model radicals for oxygen and nitrogen atoms at a position α to the radical center (MeCHNH$_2$ and MeCHOH, see Figure S6 and data in the Supporting Information) in their optimal geometry and an enforced orthogonal geometry show that nitrogen stabilizes the neighboring radical by more than 4 kcal/mol relative to oxygen (in the optimal geometry, the π lone pair of the oxygen atom is overlapping the singly occupied orbital whereas in the orthogonal geometry it is the σ lone pair which, due to its low energy, is not expected to contribute significantly to the radical stabilization).

Despite the lesser efficiency of oxygen, the remarkable and exhaustive work of Procter et al. on cyclic lactones nicely demonstrates this principle for oxygen.[12−19] It is possible that in lactones this lesser efficiency is compensated for by having two oxygen atoms flanking the radical center (eq S2, Supporting Information). It was shown that (a) the electron transfer to the carbonyl group is favored when the ring oxygen is suitably situated (six membered ring) to stabilize the odd electron on the carbonyl carbon[12,13] and (b) after protonation on the oxygen, the radical which is now stabilized by two oxygen atoms, undergoes predominantly typical radical reactions[16,17] rather than accepting an additional electron, although the reactions are sometimes carried out in the presence of a large excess (6−8 equiv) of SmI$_2$.[15]

It should be emphasized that acyclic esters normally do not undergo reduction by SmI_2. This is because in order to benefit from the stabilization of the odd electron by the π-lone pair on the oxygen, the free rotation must be frozen, and apparently, the entropic cost is too high to permit this option.

It is worth noting that the resistance of the radical to accept the second electron is not an absolute property but is always relative to the other options. Thus, in the absence of a more attractive reaction path, the radical will accept an electron. An example of this is the lactone carrying an additional ester group where a deuteriolactol was obtained.[18,19] In this case and in the Meldrum acid reactions,[14] the inductive effect of the neighboring group probably contributes some driving force to the radical conversion into a carbanion. In addition, the ring may be flexible enough to avoid to some degree the overlap which results in the four-electron destabilization.

Finally, the reactivity of a lone-pair-stabilized radical should be discussed. In principle, one may argue that because of its stabilization, the reactivity of this type of radical may be relatively low. A more detailed analysis shows that this is not necessarily the case. In symmetric radical combination reactions its reactivity will not differ much from that of the unperturbed radical. In additions to double bonds, its reactivity depends on the nature of the transition state. In early transition states, this radical is expected to be nucleophilic and more reactive than the unperturbed radical. However, in the case of a late transition state, it will resemble the reactivity of the unperturbed radical. In terms of valence bond this is because the stabilization stemming from the partial double bond between the atoms carrying the three electrons is lost at this late transition state. In electrophilic radical additions to double bonds, in an early transition state, the stabilized radical will be more sluggish than the normal radical, and in a late transition state it will display a similar reactivity.

A real challenge left for the synthetic chemist is to find a lone pair containing group which can be added and removed in a way similar to a protecting group to channel the SmI_2 reduction to the appropriate reaction path.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Equations S1 and S2, Figures S1−S6, computed spectra, Gaussian archives, complete ref 8, experimental section, and NMR and mass spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews on SmI_2 over the past 10 years, see: (a) Szostak, M.; Procter, D. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 9238. (b) Sautier, B.; Procter, D. J. *Chimia* **2012**, *66*, 399. (c) Procter, D. J.; Flowers, R. A., II; Skrydstrup, T. *Organic Synthesis Using Samarium Diiodide: A Practical Guide*; The Royal Society of Chemistry: Cambridge, U.K., 2010. (d) Concellón, J. M.; Rodríguez-Solla, H.; Concellón, C.; Amo, V. *Chem. Soc. Rev.* **2010**, *39*, 4103. (e) Honda, T. *Heterocycles* **2010**, *81*, 2719. (f) Nakata, T. *Chem. Soc. Rev.* **2010**, *39*, 1955. (g) Nicolaou, K. C.; Ellery, S. P.; Chen, J. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 7140. (h) Gopalaiah, K.; Kagan, H. B. *New J. Chem.* **2008**, *32*, 607. (i) Ichikawa, S. *Chem. Pharm. Bull.* **2008**, *56*, 1059. (j) Faugeroux, V.; Genisson, Y. *Curr. Org. Chem.* **2008**, *12*, 751. (k) Jung, D. Y.; Kim, Y. H. *Synlett* **2005**, 3019. (l) Concellón, J. M.; Rodrıǵuez-Solla, H. *Chem. Soc. Rev.* **2004**, *33*, 599. (m) Dahlén, A.; Hilmersson, G. *Eur. J. Inorg. Chem.* **2004**, 3393. (n) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371. (o) Szostak, M.; Fazakerley, N. J.; Parmar, D.; Procter, D. J. *Chem. Rev.* **2014**, *114*, 5959. (p) Choquette, K. A.; Flowers, R. A. Sm and Yb Reagents. In *Comprehensive Organic Synthesis*, 2nd ed.; Molander, G. A., Knochel, P., Eds.; Elsevier: Oxford, 2014; Vol. *1*, pp 279−343.

(2) (a) Amiel-Levy, M.; Hoz, S. *J. Am. Chem. Soc.* **2009**, *131*, 8280. (b) Amiel-Levy, M.; Hoz, S. *Chem.—Eur. J.* **2010**, *16*, 805.

(3) Hutton, T. K.; Muir, K. W.; Procter, D. J. *Org. Lett.* **2003**, *5*, 4811.

(4) (a) Rao, C. N.; Hoz, S. *J. Am. Chem. Soc.* **2011**, *133*, 14795. (b) Rao, C. N.; Hoz, S. *J. Org. Chem.* **2011**, *76*, 9438.

(5) Yella, R.; Hoz, S. *Org. Lett.* **2013**, *15*, 5262.

(6) Hasegawa, E.; Curran, D. P. *Tetrahedron Lett.* **1993**, *34*, 1717.

(7) Skene, W. G.; Scaiano, L. C.; Cozens, F. L. *J. Org. Chem.* **1996**, *61*, 7918.

(8) GAUSSIAN 03, revision A.04; Gaussian Inc., Pittsburgh, 2003.

(9) Frost, A. A.; Pearson, R. G. *Kinetics and Mechanism*; Wiley: New York, 1961.

(10) Hoz, S. *J. Org. Chem.* **1982**, *47*, 3545−3547.

(11) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books: Sausalito, CA, 2006; p 831.

(12) (a) Kamochi, Y.; Kudo, T. *Chem. Lett.* **1993**, 1495. (b) Duffy, L. A.; Matsubara, H.; Procter, D. J. *J. Am. Chem. Soc.* **2008**, *130*, 1136.

(13) Parmar, D.; Duffy, L. A.; Sadasivam, D. V.; Matsubara, H.; Bradley, P. A.; Flowers, R. A., II; Procter, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 15467.

(14) Guazzelli, G.; De Grazia, S.; Collins, K. D.; Matsubara, H.; Spain, M.; Procter, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 7214.

(15) Collins, K. D.; Oliveira, J. M.; Guazzelli, G.; Sautier, B.; De Grazia, S.; Matsubara, H.; Helliwell, M.; Procter, D. J. *Chem.—Eur. J.* **2010**, *16*, 10240.

(16) Parmar, D.; Matsubara, H.; Price, K.; Spain, M.; Procter, D. J. *J. Am. Chem. Soc.* **2012**, *134*, 12751.

(17) Sautier, B.; Lyons, S. E.; Webb, M. R.; Procter, D. J. *Org. Lett.* **2012**, *14*, 146.

(18) Szostak, M.; Collins, K. D.; Fazakerley, N. J.; Spain, M.; Procter, D. J. *Org. Biomol. Chem.* **2012**, *10*, 5820.

(19) Szostak, M.; Spain, M.; Choquette, K. A.; Flowers, R. A., II; Procter, D. J. *J. Am. Chem. Soc.* **2013**, *135*, 15702.