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Should Dithiophosphinate Esters Function as RAFT Agents?

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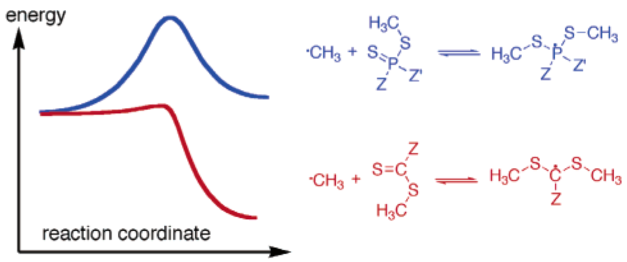
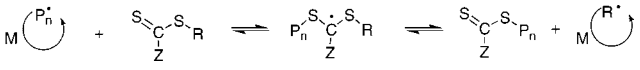
ABSTRACT



High-level ab initio calculations indicate that $^{\bullet}CH_3$ addition to the sulfur center of S═P(Z)(Z′)SCH$_3$ (Z,Z′ = CH$_3$, CN, OCH$_3$, Ph) is considerably less exothermic than addition to the corresponding RAFT agents, S═C(Z)SCH$_3$. This suggests that dithiophosphinate esters may have only limited use in controlling free-radical polymerization, but should make excellent radical chain carriers in organic synthesis. The results cast doubt on the notion that phosphoranyl radicals are more "intrinsically" stabilized than carbon-centered radicals.

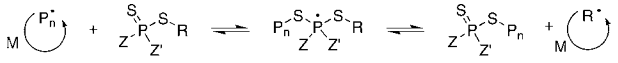
The reversible-addition-fragmentation-transfer (RAFT) process is an important new method for controlling the molecular weight and architecture in free-radical polymerization.[1] The process can be used to generate complex macromolecular architectures such as comb, star, and block copolymers for use in bioengineering and nanotechnology applications. Although RAFT has been applied to a wide range of monomers, the design of new agents for the control of monomers with highly stabilized or unstabilized propagating radicals remains a challenge.

In the RAFT process, control is achieved by protecting the majority of the propagating species from bimolecular termination through their reversible trapping into a dormant thiocarbonylthio compound as follows:



A delicate balance of the rates of these various reactions is required, so as to ensure that the dormant species is orders of magnitude greater in concentration than the active species, and the exchange between the two forms is rapid. The reactivity of the RAFT agent (and stability of the RAFT-adduct radical) must thus be tailored to match the reactivity and stability of the polymeric propagating radical; finding RAFT agents with suitable properties can be a limiting factor in controlling the polymerization of some types of monomer.

Recently it was suggested that dithiophosphinate esters might be used in place of dithioesters in the RAFT process.[2] The propagating radical would add to the sulfur center of the P═S bond, generating a phosphoranyl radical (instead of a carbon-centered radical) as the intermediate.[2]



It may be expected that radical addition to dithiophosphinates is more favorable than radical addition to dithioesters since phosphoranyl radicals are considered to be more stabilized

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(1) (a) Le, T. P. T.; Moad, G.; Rizzardo, E.; Thang, S. H. PCT Int. Appl. WO 9801478 A1 980115 1998; *Chem. Abstr.* **1998** *128*, 115390. (b) Charmot, D.; Corpart, P.; Michelet, D.; Zard, S. Z.; Biadatti, T. PCT Int. Appl. WO 9858974, 1998; *Chem Abstr.* **1999**, *130*, 82018.

(2) Gigmes, D.; Bertin, D.; Marque, S.; Guerret, O.; Tordo, P. *Tetrahedron Lett.* **2003**, *44*, 1227.

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than carbon-centered radicals,[3] and P═S bonds are believed to be weaker than C═S bonds.[4] Under such circumstances, dithiophosphinate esters might be expected to be suitable for controlling polymerizations involving highly stabilized propagating radicals (as in α-methylstyrene polymerization), and could potentially expand the scope of the RAFT process.

To date there is only limited data on the performance of dithiophosphinate esters as control agents. Gigmes et al.[2] reported that styrene polymerization could be controlled using $S{=}P(SCH(CH_3)Ph)_3$ and $S{=}P(Ph)_2SCH(CH_3)Ph$. Although no molecular weight distributions were provided, they noted that, in the presence of the agents, the molecular weight increased with conversion. However, the behavior was by no means linear, as should have been expected in a true living polymerization. In particular, there was an initial increase to very high molecular weight, more consistent with hybrid behavior. It is clear that more information on the reactivity of these agents is required, to assist in the optimization of the process.

To examine the suitability of P═S based RAFT agents, we performed high-level ab initio molecular orbital calculations[5] on the simple model system:

$$^{\bullet}CH_3 + S{=}P(CH_3)_2SCH_3 \rightarrow CH_3SP^{\bullet}(CH_3)_2SCH_3 \quad (1)$$

Surprisingly, we found that this reaction was considerably less exothermic, and proceeded with a considerably higher reaction barrier than its C═S analogue:

$$^{\bullet}CH_3 + S{=}C(CH_3)SCH_3 \rightarrow CH_3SC^{\bullet}(CH_3)SCH_3 \quad (2)$$

For the P═S agent the calculated (0 K) reaction barrier is 50.8 kJ mol^{-1} and the enthalpy is −7.4 kJ mol^{-1}; for the corresponding C═S agent the barrier and enthalpy are 10.6 and −64.2 kJ mol^{-1}, respectively.[6b] Thus the addition to the P═S bond is nearly 60 kJ mol^{-1} *less* exothermic, despite the fact that its phosphoranyl radical product is supposedly 120 kJ mol^{-1} *more* stabilized[7]—that is, we have a 180 kJ mol^{-1} discrepancy (see Figure 1).

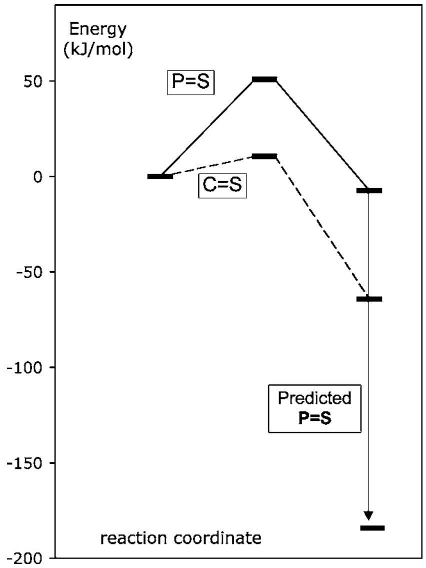

Figure 1. Free energy diagrams (0 K, kJ mol^{-1})[5] for methyl radical addition to the sulfur center of $S{=}P(CH_3)_2SCH_3$ ("P═S") and $S{=}C(CH_3)SCH_3$ ("C═S"), showing also the predicted relative exothermicity of the S═P addition, on the basis of the greater radical stabilization energy of the product radical.

Since reactions 1 and 2 both consume a methyl radical and produce a C−S σ bond, the only other principal difference between them is the fact that reaction 1 destroys a P═S double bond, while reaction 2 destroys a C═S double bond. However, as noted above, a previous study had concluded that P═S double bonds are approximately 50 kJ mol^{-1} *weaker* than C═S double bonds,[4] and thus on this basis reaction 1 should also have been thermodynamically favored. It thus seems that phosphoranyl radicals are significantly *less* stabilized than carbon-centered radicals and/or that the P═S bonds are significantly stronger than C═S bonds.

To establish the generality of this result, we next compared methyl radical addition to the sulfur center of the P═S and C═S bonds in other RAFT-related systems, $S{=}P(Z)(Z')SCH_3$ and $S{=}C(Z)SCH_3$ (for Z, Z′ = CH_3, CN, OCH_3, and Ph).[5,6] We also examined the simpler non-RAFT systems, $S{=}P(CH_3)_3$ and $S{=}C(CH_3)_2$. The barriers and enthalpies for these reactions, together with the radical stabilization energies (RSEs) of the product phosphoranyl and carbon-centered radicals, are summarized in Table 1. It is clear that, for all of the substituents considered, radical addition to P═S bonds occurs with higher reaction barriers and lower exothermicities than addition to C═S bonds, despite the apparent greater stability of the product phosphoranyl radicals.

To understand these unexpected results, we need to examine the measurement of π bond strength and radical stability more carefully. One typically measures the "stability" of a radical on the basis of its radical R$^{\bullet}$ stabilization energy (RSE):

$$R^{\bullet} + H{-}CH_4 \rightarrow R{-}H + {}^{\bullet}CH_3 \quad (3)$$

This compares the energies of the R$^{\bullet}$ and $^{\bullet}CH_3$ radicals, using

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[3] Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*; Masson: Paris, France, 1995.

[4] Schmidt, M. W.; Truong, P. H.; Gordon, M. S. *J. Am. Chem. Soc.* **1987**, *109*, 5217.

[5] Calculations were performed at the G3(MP2)-RAD level of theory, using B3-LYP/6-31G(d) optimized geometries and scaled B3-LYP/6-31G(d) zero-point vibrational energy. Full details of the calculations are provided in the Supporting Information.

[6] G3(MP2)-RAD barriers, enthalpies, and RSEs for the thiocarbonylthio systems were taken from the following: (a) Coote, M. L.; Wood, G. P. F.; Radom, L. *J. Phys. Chem. A* **2002**, *106*, 12124. (b) Coote, M. L.; Radom, L. *J. Am. Chem. Soc.* **2003**, *125*, 1490. (c) Coote, M. L.; Radom, L. *Macromolecules* **2004**, *37*, 590. (d) Coote, M. L.; Henry, D. J. *Macromolecules* **2005**, *38*, 1415. (e) Hodgson, J. L.; Coote, M. L. *J. Phys. Chem. A*. In press.

[7] If we define radical stabilization energies (RSEs) from R−H BDEs in the usual manner (i.e., as in eq 3), the calculated RSE of the phosphoranyl product of the model system in reaction 1 is 180.6 kJ mol^{-1} at the G3(MP2)-RAD level of theory, while that of the carbon-centered radical product of the model system in reaction 2 is just 59.9 kJ mol^{-1}.

Table 1. Barriers and Enthalpies for ${}^{\bullet}CH_3$ Addition to $S{=}P(Z)(Z')SCH_3$ and $S{=}C(Z)SCH_3$, and Radical Stabilization Energies (RSEs)[a] of the Corresponding Product Radicals (0 K, kJ mol^{-1})[5,6]

		${}^{\bullet}CH_3 + S{=}P(Z)(Z')SCH_3$			${}^{\bullet}CH_3 + S{=}C(Z)SCH_3$		
Z	Z′	$\Delta H^{\ddagger}$	ΔH	RSE	$\Delta H^{\ddagger}$	ΔH	RSE
CH_3	CH_3	50.8	−7.4	180.6	10.6	−64.2	59.9
OCH_3	CH_3	56.0	13.6	157.9	24.2	−29.2	58.5
CN	CH_3	43.9	−25.4	189.8		−122.9	99.1
Ph	CH_3	53.8	−3.3	196.9	5.5	−95.2	96.3
OCH_3	OCH_3	51.1	9.0	139.0			
CN	CN	35.2	−49.7	166.1			
OCH_3	CN	48.1	−9.5	148.1			
$S{=}P(CH_3)_3$ and $S{=}C(CH_3)_2$		72.8	30.9	174.0[b]	7.1	−82.8	45.8

[a] RSEs defined as the energy change of the following reaction: $R^{\bullet} + CH_4 \rightarrow R{-}H + {}^{\bullet}CH_3$. [b] From ref 6e.

the corresponding hydrides to balance the reaction. When $R^{\bullet}$ is a phosphoranyl radical, this reaction is highly endothermic, implying that phosphoranyl radicals are more stabilized than ${}^{\bullet}CH_3$. However, this of course assumes that the difference in the stabilities of the P−H and C−H bonds is negligible. The question thus arises, are phosphoranyl radicals more inherently stabilized than carbon-centered radicals, or do their large RSEs merely reflect the lower stability of the P−H versus C−H bonds?

Recently, we provided evidence to suggest that phosphoranyl radicals may actually be less "intrinsically" stabilized than carbon-centered radicals.[6e] We showed that the following α-scission reaction was weakly exothermic:

$$ {}^{\bullet}P(CH_3)_4 \rightarrow P(CH_3)_3 + {}^{\bullet}CH_3 \tag{4} $$

This is despite the fact that a P−C bond is broken and no new bonds are formed. It would appear that the energy cost of breaking the P−C bond is supplied by the conversion of the phosphoranyl radical into a *more stabilized* ${}^{\bullet}CH_3$ radical. This lower inherent stability of the phosphoranyl radicals may help to explain the low reactivity of the dithiophosphinate esters toward methyl radical addition.

However, this is only part of the story, and the strengths of the C═S and P═S double bonds also need to be examined more carefully. As noted above, a previous study had concluded that P═S bonds were considerably weaker than C═S double bonds.[4] However, this conclusion was based on a comparison of the corrected hydrogenation energies of $H_2C{=}S$ and $HP{=}S$. When the strengths of the P═S and C═S double bonds in $S{=}P(CH_3)_2SCH_3$ and $S{=}C(CH_3)SCH_3$ are calculated using the same thermodynamic cycle, the reverse trend is actually obtained.[8] That is, it appears that, in dithiophosphinate esters, the P═S bond is stronger than the corresponding C═S double bond of dithioesters, and this also contributes to their lower reactivity.

In fact this is somewhat of an oversimplification because, like radical stability, double bond strength is difficult to measure unambiguously. In the present work, we adopted the corrected hydrogenation energies approach.[4] In essence one calculates the energy to destroy the double bond (A═B, say) by hydrogenation to the corresponding saturated compound (in this case, HA−BH). The energy of this reaction is then corrected by subtracting the energy of the H−H bond that is also lost, and adding the energies of the H−A and H−B bonds that are formed in the process. The energies of the H−A and H−B bonds are approximated by using the bond dissociation energies of the corresponding saturated compound.[4] This raises a problem. If one estimates the differing strengths of the P−H and C−H bonds on the basis of their relative bond dissociation energies, we return to the question as to whether the lower P−H BDE reflects its reduced bond strength, or merely the greater stability of the $P^{\bullet}$ versus the $C^{\bullet}$ radical. As noted above, it seems likely that the $P^{\bullet}$ radicals are intrinsically less stabilized than the $C^{\bullet}$ radicals. If this were the case, the relative stability of the P−H versus C−H bond would be overestimated by their relative BDEs. As a result, the relative strength of the P═S double bond would also be overestimated compared with C═S, though it is difficult to determine the extent to which this occurs.

Nonetheless, there are reasonable chemical grounds for supposing that the P═S bonds in the dithiophosphinate esters are more stable to radical addition than the C═S bonds in the dithioesters. The molecular orbitals corresponding to the double bonds of $S{=}P(CH_3)_2SCH_3$ and $S{=}C(CH_3)SCH_3$ are shown in Figure 2. Whereas the C═S bond appears to be a genuine π bond, the P═S bond is closer to an ionic bond. Thus, when ${}^{\bullet}CH_3$ attacks the "double bond" of the dithiophosphinate ester system, it effectively has to disrupt a lone pair of electrons. The energy cost of this might reasonably be expected to be greater than the cost of the $\pi{-}\pi^*$ transition of the dithioester. Indeed, the vertical singlet triplet gaps of $S{=}P(CH_3)_2SCH_3$ and $S{=}C(CH_3)SCH_3$ are 4.5 and 2.6 eV, respectively.[5]

The role of this ionic configuration in stabilizing the S═P bond is further supported by the observation that the dithiophosphinate esters that are substituted with groups that stabilize the positive charge on phosphorus (such as methoxy

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[8] Using the same thermodynamic cycle as in ref 4, our calculated P═S and C═S double bond energies are 295.6 and 217.3 kJ mol^{-1} at the G3-(MP2)-RAD level of theory.

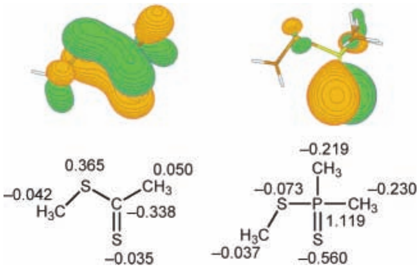

Figure 2. B3-LYP/6-311+G(3df,2p) NBO charge distributions within $S{=}C(CH_3)SCH_3$ and $S{=}P(CH_3)_2SCH_3$, and also contour plots of the orbitals corresponding to their double bonds (the HOMO-2 and HOMO, respectively).

and phenyl) have higher barriers and smaller exothermicities than those substituted with groups that destabilize it (such as CN).

Regardless of its origin, the low reactivity of dithiophosphinate esters toward radical addition has important synthetic implications. From a polymerization perspective, it appears that dithiophosphinate esters may have only limited use as RAFT agents. As noted above, for adequate control of free-radical polymerization, it is important to design agents for which the exchange between the dormant and active forms is rapid. This entails that the rate of addition of the propagating radical to the RAFT agent is fast, when compared with the propagation rate.[9] Even for the reactive methyl radical, both the addition and fragmentation barriers are very high; for most polymeric propagating radicals one might expect even slower addition rates. Although in principle one might lower the barrier to addition through the stabilization of the product phosphoranyl radical, this would have the concurrent effect of increasing the fragmentation barriers (which are already very high). However, by substituting the agents with substituents that destabilize the $S^{-}{-}P^{+}$ configuration of the double bond, the reactivity may be maximized. Moreover, one might expect that barriers to addition would be lower for electrophilic radicals, such as in acrylonitrile polymerization. Further work to explore this possibility is now underway.

Although a disadvantage for controlling free-radical polymerization, the low reactivity of dithiophosphinate esters is an advantage for an alternative synthetic application. Phosphoranyl radicals can function as radical chain carriers in processes of the form[10,11]

$$RS^{\bullet} + PZ_3 \rightarrow RSP^{\bullet}Z_3 \rightarrow R^{\bullet} + S{=}PZ_3$$

Provided the substituents on the phosphine are chosen carefully, the reaction provides a highly selective and efficient source of alkyl radicals. The relatively low rate of radical addition to the product dithiophosphinate ester ensures that the β-scission step is virtually irreversible, and that the dithiophosphinate esters do not function as radical sinks for any other species in the process.

In conclusion, methyl radical addition to the sulfur center of P=S double bonds occurs with considerably higher reaction barriers and lower exothermicities than the corresponding additions to C=S bonds. It seems likely that this is due in part to the lower inherent stability of the phosphoranyl radical product, and in part to the greater ionic character of the P=S double bond. The present results indicate that dithiophosphinate esters may have only limited use in controlling radical polymerization, though it may be possible to optimize their reactivity by using electron-withdrawing substituents at phosphorus. However, their low reactivity to radical addition is an advantage in the synthetic use of phosphoranyl radicals as radical chain carriers in organic synthesis.

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Supporting Information Available: Full details of the calculations, including B3-LYP/6-31G(d) optimized geometries for all species. This material is available free of charge via the Internet at http://pubs.acs.org.

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[9] Although one could compensate for the slow addition rate by increasing the RAFT agent concentration, this serves to decrease the molecular weight of the polymer.

[10] For reviews of this chemistry, see, for example: (a) Roberts, B. P. *Adv. Free-Radical Chem.* (*London*) **1980**, *6*, 225. (b) Bentrude, W. G. *Acc. Chem. Res.* **1982**, *15*, 117.

[11] For a recent synthetic application, see, for example: Cai, Y.; Roberts, B. P. *Tetrahedron Lett.* **2001**, *42*, 4581.