Free-Radical Polymerization for Narrow-Polydispersity Resins. Semiempirical Molecular Orbital Calculations as a Criterion for Selecting Stable Free-Radical Reversible Terminators

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ABSTRACT: Semiempirical molecular orbital calculations at the AM1 and PM3 levels have been used to model stable free-radical-mediated living polymerization reactions. These calculations predict that in the living free-radical polymerization, the reversible terminator of the growing polymer radical must have a calculated bond dissociation enthalpy of less than 35 kcal/mol in order to achieve reasonable rates of chain propagation. Furthermore, the calculations also correctly predict that reversible terminators such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) have an endothermic enthalpy of reaction with styrene monomer and, therefore, are not able to initiate new chains, a prerequisite for narrow polydispersity in these systems. Calculations have been performed on 21 possible reversible terminator structures. One of these reversible terminators, di-*tert*-butyl nitroxide, was predicted to have a lower bond dissociation enthalpy than the benchmark TEMPO reversible terminator. Experiments have confirmed that under comparable reaction conditions, the di-*tert*-butyl nitroxide-mediated reaction proceeds to completion more rapidly than the comparable TEMPO reaction, consistent with the predictions of the molecular orbital calculations.

Introduction

The development of a living free-radical polymerization that enables the preparation of narrow-polydispersity resins and controlled block length polymers remains a key challenge in polymer chemistry.[1]

Living polymer systems, as defined by Webster,[2] have three primary characteristics. First of all, assuming that the initiator is 100% efficient, the ultimate molecular weight is given by eq 1, where D_p is the degree of polymerization, [M] is the initial concentration of monomer, and [I] is the concentration of growing polymer (chains generated by the initiator). Furthermore, the polydispersity is narrow and is given by eq 2 in the ideal case. Finally, in contrast to conventional free-radical polymerization reactions, where high molecuar weight material is formed early in the reaction and the molecular weight remains relatively constant as a function of conversion, in a living polymerization the molecular weight increases linearly as a function of the conversion.

$$D_p = [M]/[I] \qquad (1)$$

$$PD = 1 + 1/D_p \qquad (2)$$

In practice, all living polymerizations deviate to some degree from this ideal case.[2,3] This deviation occurs for a variety of reasons. For example, initiation does not occur at precisely the same time for all chains. Initial mixing problems may lead to inhomogeneities in concentration which can lead to differential growth rates for polymer chains. Equilibria between active and inactive forms are frequently present.[3] Finally, the presence of minute quantities of impurities can lead to some chain termination and the formation of dead polymer. Ultimately, these deviations from an ideal, living system lead to a broadening of the polydispersity given in eq 2. The deviation of the polydispersity from the ideal value may be regarded as a metric for measuring the degree to which a quasiliving polymerization reaction approaches the ideal living case.

An important milestone in the development of living *free-radical* polymerization reactions was the discovery of iniferter reactions. The term "iniferter", coined by Otsu et al.,[4] is derived from *ini*tiation–trans*fer*–*ter*mination and is illustrated by the dithiocarbamate system shown in Scheme 1 ($X_1 = X_2 = Me_2NCS_2$). In this procedure, which relies primarily on photochemical initiation, the dithiocarbamate radical serves both as an initiator of new chains (reaction 2) and a reversible trapping agent (reactions 3 and 4). The living nature of this reaction has been demonstrated[5] by block copolymer formation.

Although the iniferter reaction demonstrates some of the characteristics of a living polymerization such as a linear increase of molecular weight with time, there are also a number of deficiencies. For example, there is a significant loss of active end groups from the living polymer and reequilibration to the dithiuram initiator during the course of the reaction.[6] Furthermore, by the very nature of the iniferter mechanism, the dithiocarbamate radicals can initiate new chains throughout the course of the reaction, albeit very slowly.[5,6] As a consequence, the reported polydispersities are relatively large and a substantial amount of homopolymer is formed along with block copolymer.[5]

The development of a living free-radical reaction that meets the challenging test of providing resins with narrow polydispersities requires the design of reversible termination agents that balance the competing requirements of rapid propagation with *no new initiation* once all of the living chains have been generated. Semiempirical molecular orbital calculations, coupled with experimental investigations, can provide substantial direction in the selection of these reversible terminator compounds.

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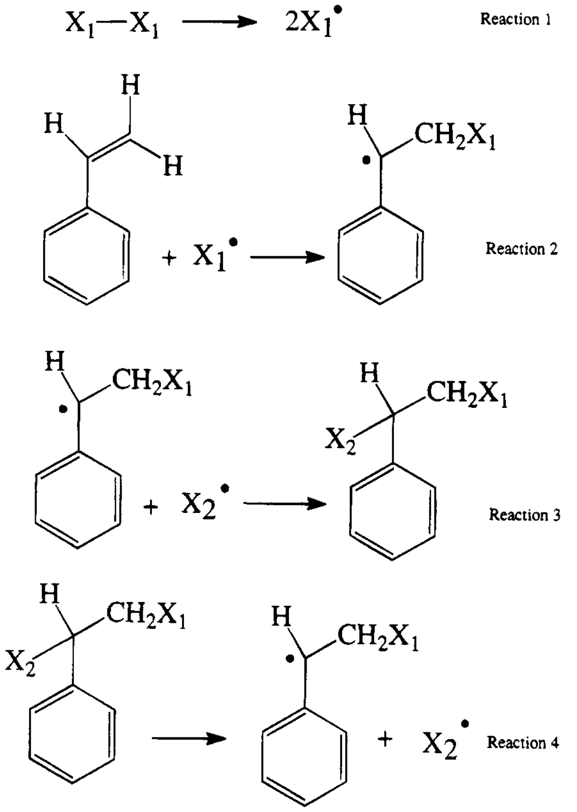
Scheme 1



Calculations and Experimental Section

Semiempirical molecular orbital calculations were performed using the MOPAC program (version 6.0) on a Silicon Graphics 4D/480 workstation. All AM1 and PM3 geometries were optimized until the gradient norm was less than 0.01 kcal mol^{-1} $Å^{-1}$ unless noted otherwise. The half-electron formalism of Dewar et al.[7] was used to calculate the open-shell structures. All calculations were carried out using the keyword PRECISE.

Standard reaction conditions for the preparation of narrow-polydispersity resins by a stable free-radical polymerization process have been described previously.[8,9] In parallel, bulk polymerization reactions, nitroxide (0.58 mmol) (2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or *tert*-butyl nitroxide) and benzoyl peroxide (BPO) (0.41 mmol) were heated together in styrene (87.2 mmol) at 95 °C for 3.5 h, followed by heating at 123 °C for 6 h. Aliquots were taken every 1 h once the temperature had reached 123 °C, and the molecular weights were determined by gel permeation chromatography (GPC) on a Waters/Millipore liquid chromatograph equipped with a Waters Model 510 pump, Ultrasytragel columns of pore size 10^4, 2 × 500, and 100 Å, and a Waters 410 differential refractometer. Polystyrene standards were used for calibration and tetrahydrofuran was used as the mobile phase with a flow rate of 0.8 mL/min. Percent conversions were determined by measuring the residual styrene by gas chromatography on a Perkin-Elmer SIGMA 2000 gas chromatograph equipped with a Perkin-Elmer LCl-100 laboratory computer integrator. The conversions to polymer were calculated by difference. The comparative results are reported in Table 5.

Results and Discussion

In order to design a living free-radical polymerization reaction that produces a polymer with a narrow molecular weight distribution, it is essential that at least three conditions are satisfied. First, all propagating chains must be initiated within a very short time period. Second, the chains must be captured in a reversible manner, as demonstrated in the iniferter system, so that the process does not terminate prematurely. This preserves the living nature of the reaction. Finally, during the course of stepwise chain growth, it is essential that no new chains are initiated by any of the intermediate radical species.

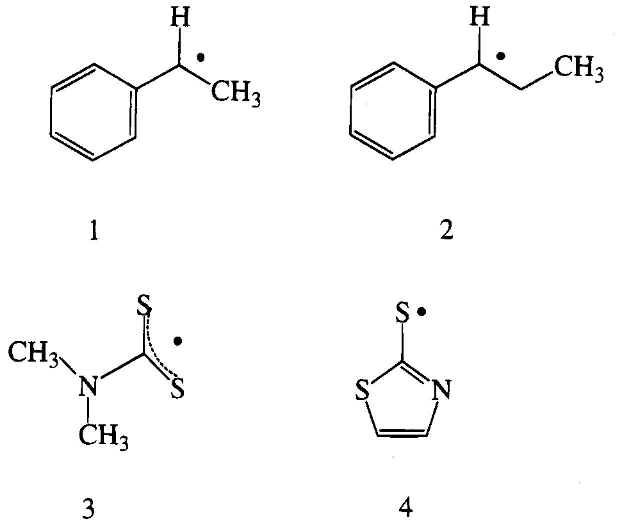
Iniferter reagents provide a partial solution to this problem in that reversible termination and block copolymer formation have been observed. However, the iniferter reaction has an inherent limitation for achieving all the features of a living reaction. By design, iniferter reagents are required to both *initiate* the polymerization and *reversibly capture* the propagating radical to ensure that the propagating species does not terminate prematurely. The initiation reaction, as shown in reaction 2 in Scheme 1, requires that the strength of the bond between the iniferter fragment X_1 and the β-carbon of styrene be reasonably high, since the energy obtained from the formation of an X_1−carbon bond must ensure that the overall free energy for the addition of the iniferter radical to the styrene vinyl group is negative. However, in order for this polymerization process to function as a living one, it is essential that the α-carbon−X_2 bond reversibly homolyze at accessible temperatures (reaction 4). That is to say, the captured carbon radical must, under the reaction conditions, spontaneously and reversibly fragment to provide enough of the active chain radical species to achieve a reasonable rate of propagation. For this second process, radical recombination (the reverse process) generally occurs without activation[10−12] (reaction 3). Thus, the strength of the α-carbon−X_2 bond determines the efficacy of the bond scission for the propagation process.

Inherently then, when a single radical intermediate is required to act as an initiator and a reversible terminator ($X_1 = X_2$), a set of offsetting requirements result. The carbon−X bond must be both strong and weak at the same time! A partial solution to this dilemma in the iniferter work was found by using photoinduced initiation.[13,14] This allows for a much stronger carbon−X_2 bond in these systems in the ground state.

An attractive solution would be to separate the initiation and propagation processes altogether. The living characteristic of the reaction can be preserved if a reversible terminator X_2 is chosen which is sufficiently reactive to capture the propagating carbon radical as an α-carbon−X_2 adduct. The reversible terminator X_2 must be chosen so that the α-carbon−X_2 bond is weak enough for thermal equilibration (reaction 4) between the free radical and the capped radical. This equilibrium must allow a sufficient concentration of free radical for propagation but not enough for irreversible chain termination. A trade-off is still required, but one that is much more manageable than the one required of an iniferter reagent. In addition, the radical X_2 must be unreactive *vis-à-vis* the initiation of new chains. Initiation is achieved with another radical (X_1) which forms a strong X_1−β-carbon bond with styrene and irreversibly binds to the polymer. The process of selecting a reversibly terminating agent could be substantially simplified if one could reliably predict the bond dissociation enthalpy shown in reaction 4 for a variety of possible structures. Molecular orbital calculations are shown to be of significant benefit in this selection process.

There are many standard radical initiators which could generate the radical X_1, for example, BPO, AIBN, etc. In order to initiate all living chain ends in a very short time span, it is essential to operate under conditions which lead to very rapid initiator fragmentation.

Chart 1



Scheme 2

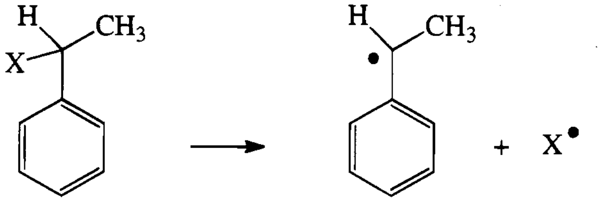


Table 1. Calculated Bond Dissociation Enthalpies for 1-Substituted Ethylbenzenes

radical fragment X	bond dissociation enthalpies (kcal/mol) AM1	PM3
$PhCO_2^•$	*a*	63
$CH_3S^•$	56	52
mercaptothiazole (**4**)	53	57
dithiocarbamate (**3**)	38	39
TEMPO (**5a**)	22	26
PROXYL (**6a**)	17	19

[a] SCF convergence problems with both RHF-half-electron and UHF methods were experienced with the benzoyloxy radical system in MOPAC. HyperChem UHF calculations gave a bond dissociation enthalpy of 58.5 kcal/mol on convergence.

Table 2. AM1 and PM3 Calculations of Electronic, Inductive, and Steric Effects on the Bond Dissociation Energies of 1-Substituted Ethylbenzenes

radical fragment X	bond dissociation enthalpies (kcal/mol) AM1	PM3
	Hammett Series	
(4-nitrophenyl)thiyl	58	57
(4-cyanophenyl)thiyl	58	57
(4-chlorophenyl)thiyl	56	55
phenylthiyl	55	54
(4-methylphenyl)thiyl	55	54
(4-methoxyphenyl)thiyl	53	52
	Steric Series	
methylthiyl	56	52
ethylthiyl	56	51
isopropylthiyl	56	53
tert-butylthiyl	56	54
	Inductive Series	
(chloromethyl)thiyl	57	53
(dichloromethyl)thiyl	58	54
(trichloromethyl)thiyl	58	56

Consequently, reaction conditions must be chosen such that the initiator half-life is very short.

The application of molecular orbital calculations to the design of reversible terminators raises three questions. What kind of calculations should be used? Can these calculations provide a sufficiently accurate estimate of bond dissociation enthalpies to allow reliable predictions? Finally, will solvent effects dominate the kinetics?

Both *ab initio* and semiempirical molecular orbital calculations have been successfully applied to radical processes.[10] However, the size of the model systems required for the present study initially compelled the use of semiempirical rather than *ab initio* methods. In order to select new reversible free-radical terminators, one would like to investigate the transition state associated with the free radical–carbon bond dissociation. However, locating a transition state is still a formidable challenge, particularly when the starting material is a closed-shell species while the products are open-shell entities. Rather than challenging the complexities of the transition state calculation, it was decided to calculate bond dissociation enthalpies with the assumption that radical recombination occurs without an activation energy.

With regards to the third question on solvent effects, radical reactions are relatively insensitive to solvent conditions and so solvent effects, on first approximation, can be ignored.[15]

The radical derived from ethylbenzene (**1**) was chosen as the model representing the polymer. Initial investigations[16] using the propylbenzene radical (**2**) indicated that the longer chain length necessitated the evaluation of many conformational minima involving the $\alpha-\beta$ carbon bond without improving the reliability of the results. The choice of **1** as the model system removed this complication. The nitroxide moiety was oriented in such a way that the N–O bond was equatorial with respect to the cyclic nitroxide (where appropriate[18]) and conformational searches using molecular mechanics and semiempirical calculations indicated that the energy of the adduct was not significantly affected by this nitroxide conformational constraint.

The bond dissociation enthalpy was estimated by calculating the heats of formation of the species shown in the reaction in Scheme 2. Subtraction of the heat of formation of the reactant from those of the products provided the bond dissociation enthalpy for the bond scission reaction.

Table 1 summarizes the results of AM1 and PM3 calculations on the bond dissociation enthalpies for a variety of systems. Initiators such as benzoyloxy radical show large (63 kcal/mol) bond dissociation enthalpies consistent with the perception that these intermediates lead to *irreversible* termination. Chain transfer reagents, represented by the methylthiyl radical, show substantially lower bond dissociation enthalpies, while iniferters (**3**) have weaker bonds still.

Attempts to decrease the iniferter–carbon bond strength by structure modification were not promising. The highly delocalized mercaptothiazole (**4**) has a substantially higher calculated bond dissociation enthalpy than iniferter **3**. Indeed, investigating the electronic, inductive, and steric effects on the strength of the sulfur–carbon bond in our model system indicated that this bond is not particularly sensitive to any of these modifications.

As shown in Table 2, PM3 calculations show a very small increase in bond dissociation enthalpy on successively substituting hydrogens in the methylthiyl radical with methyl groups. Similarly, the inductive effect of

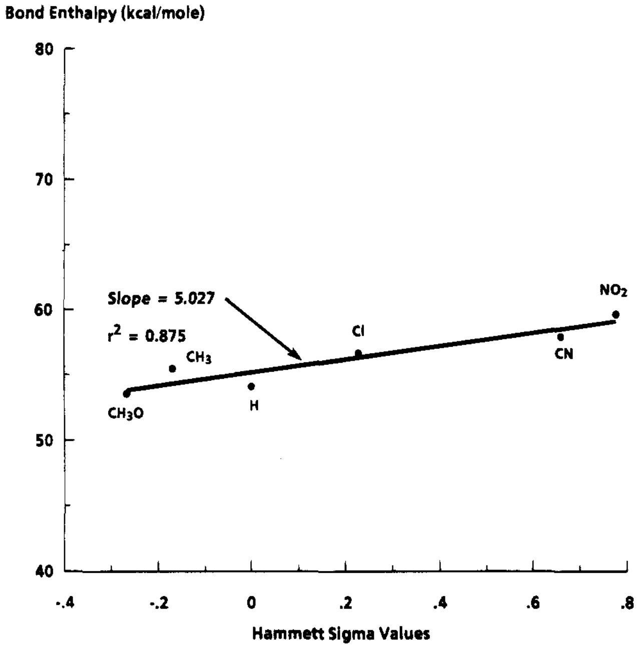


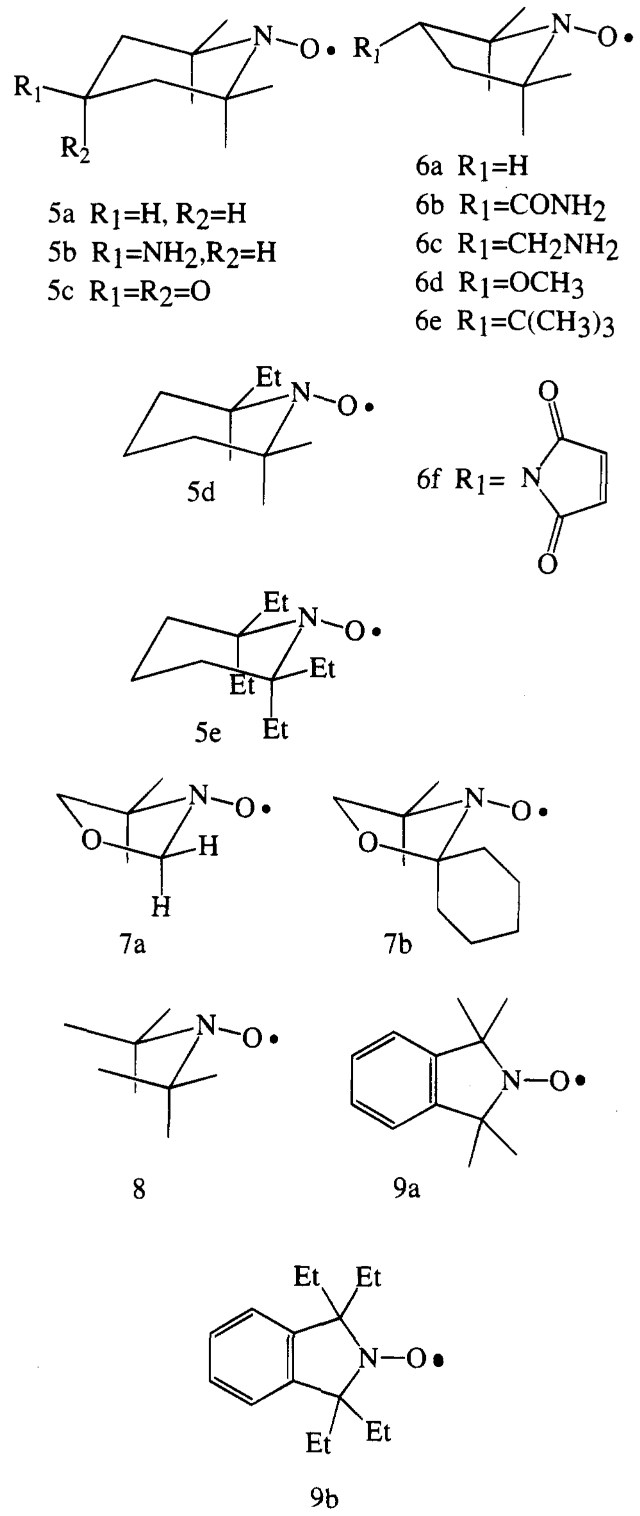
Figure 1. Plot of the bond dissociation enthalpies of substituted 1-phenylethyl phenyl sulfides.

Table 3. Calculated Reaction Enthalpies for the Addition of Various Radicals to Styrene

	reaction enthalpies (kcal/mol)	
radical fragment X	AM1	PM3
$PhCO_2^•$	*a*	−33
$CH_3S^•$	−25	−22
mercaptothiazole (**4**)	−24	−29
dithiocarbamate (**3**)	−8	−11
TEMPO (**5a**)	7	5
PROXYL (**6a**)	7	6

[a] SCF convergence problems with both RHF-half-electron and UHF methods were experienced with the benzoyloxy radical system. HyperChem UHF calculations gave a reaction enthalpy of −54.3 kcal/mol on convergence.

Chart 2



successively substituting hydrogens with chlorine atoms again only leads to an increase of bond dissociation enthalpy of 2 (AM1) and 4 kcal/mol (PM3). The bond dissociation enthalpy for the derivatives where X = (4-nitrophenyl)thiyl and X = (4-methoxyphenyl)thiyl differs by only 7 kcal/mol (Figure 1). Thus molecular orbital calculations indicate that the search for reversible terminators must focus on new classes of free radicals that are very stable, readily captured, and have no propensity for initiating new chains.

As can be seen in Table 1, very stable free radicals such as TEMPO (**5a**)[18] and PROXYL (**6a**)[18] enable very low bond dissociation enthalpies, substantially less than those obtained for the dithiocarbamate adduct (**3**).

Can these radical species initiate new chain growth? Table 3 summarizes the enthalpies of radical formation for the reaction depicted in Scheme 1 (reaction 2), that is to say, the reaction of a free radical with styrene.

The trend in Table 3 is qualitatively consistent with the experimental results obtained. The reaction of the benzoyloxy free radical with styrene is predicted to be very exothermic, as is the reaction of the radical chain transfer analog methylthiyl. The radical derived from the iniferter reagent (**3**) is less exothermic but still has a small negative enthalpy of reaction (−8 kcal/mol (AM1); −11 kcal/mol (PM3)) consistent with slow initiation of new chains. Only the nitroxyl adducts in this series are predicted to be endothermic with regards to the initiation reaction.

Experimental verification of the TEMPO/styrene system indeed has shown that the initial semiempirical predictions were correct[8,9,16] and that a living polymerization could be achieved. From a design perspective, the encouraging bond dissociation enthalpies were extremely valuable in providing the impetus to continue the investigation on this system even though early experimental results were not encouraging.[16]

In summary, semiempirical molecular orbital calculations can be used to identify stable free-radical sub-

Table 4. Calculated Bond Dissociation and Reaction Enthalpies for a Variety of Heterocyclic Stable Free Radicals

	bond dissociation enthalpies (kcal/mol)		reaction enthalpies (kcal/mol)	
radical fragment X	AM1	PM3	AM1	PM3
PhNNO (at O)	28	34	4	−1
PhNNO (at N)	14	31	17	0
4-amino-TEMPO (**5b**)	22	26	5	2
4-oxo-TEMPO (**5c**)	19	24	6	4
2,2,6-trimethyl-6-ethyl-1-piperidinyloxy (**5d**)	13	20	6	1
2,2,6,6-tetraethyl-1-piperidinyloxy (**5e**)	14	26	10	1
3-carbamoyl-PROXYL (**6b**)	17	21	2	3
3-(aminomethyl)PROXYL (**6c**)	18	20	7	6
3-methoxy-PROXYL (**6d**)	23	26	7	6
3-*tert*-butyl-PROXYL (**6e**)	23	27	7	7
3-maleimido-PROXYL (**6f**)	23	27	7	6
DOXYL (**7a**)	27	29	−1	8
2-cyclohexyl-DOXYL (**7b**)	25	28	2	−1
di-*tert*-butyl nitroxide (**8**)	17	22	8	5
tetramethylisoindoline nitroxide (**9a**)	24	26	7	7
tetraethylisoindoline nitroxide (**9b**)	23	26	7	9

Table 5. Comparative Reaction Profiles of TEMPO and Di-*tert*-butyl Nitroxide

	di-*tert*-butyl nitroxide (**8**)				TEMPO (**5**)			
reacn time (h)	conv[a] (%)	M_n	M_w	M_w/M_n	conv[a] (%)	M_n	M_w	M_w/M_n
1	nd	1432	1987	1.38	nd	141	297	2.11
2	15	4758	6503	1.37	nd	1654	2174	1.31
3	22	8993	11831	1.32	nd	4959	6006	1.21
4	36	13839	16556	1.20	24	3500	4331	1.24
5	63	21153	25887	1.22	49	8762	10306	1.18

[a] The designation nd indicates that these conversions were not determined.

strates with bond dissociation enthalpies consistent with a living system. If semiempirical molecular orbital calculations can correctly predict changes in reactivity of living free-radical systems, then this will provide additional verification of the validity of the calculations.

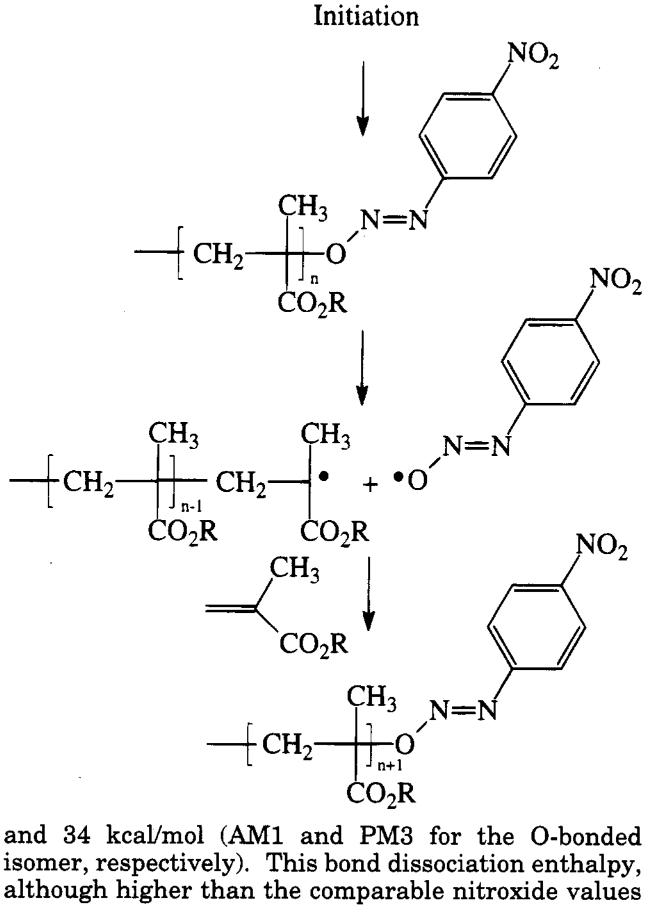
Having initially established the usefulness of semiempirical AM1 and PM3 calculations in predicting potential stable free-radical coreagents, it was of interest to apply this methodology to a large variety of systems and then test the predictions experimentally. The calculated bond dissociation enthalpies for a wide variety of potential reversible terminators are shown in Table 4. Calculated bond dissociation enthalpies of less than 35 kcal/mol indicate that thermal dissociation would occur more rapidly than the dithiocarbamate iniferter system, and as a consequence these reagents are predicted to provide propagation rates in excess of those shown in the iniferter test case and act as reversible trapping agents.

The commercially available di-*tert*-butyl nitroxide reversible terminator (**8**) was chosen for additional experimental study since this particular reversible terminator is predicted to have a lower bond dissociation enthalpy than TEMPO by both AM1 and PM3 methods (see Table 4).

Parallel reactions of di-*tert*-butyl nitroxide and TEMPO were conducted under comparable conditions. Aliquots were removed and characterized at 1 h intervals. The results of this comparison are shown in Table 5. As predicted by the molecular orbital calculations, di-*tert*-butyl nitroxide provides a significantly faster polymerization reaction (more than 3 times faster per growing chain) while maintaining the narrow polydispersity first observed with the TEMPO system.

Finally, this analysis was extended to living systems in the literature. Druliner[17] noted that (arylazo)oxy radicals can provide a living polymerization with methyl methacrylate (MMA) as the monomer. Calculations suggest that for this system, depicted in Scheme 3, the bond dissociation energy calculated for PhNNO(•) is 28 and 34 kcal/mol (AM1 and PM3 for the O-bonded isomer, respectively). This bond dissociation enthalpy, although higher than the comparable nitroxide values is lower than the iniferter value and so is consistent with the observation that this system gives rise to a living system with block copolymer formation.

Scheme 3



Conclusions

Semiempirical calculations are extremely valuable in identifying new stable free radicals for living systems.

Bond dissociation enthalpies, in conjunction with enthalpies of radical addition, provide a rapid and valuable screening procedure.

Initially in our own work, these calculations proved their worth in bolstering our confidence in the validity of the reversible terminator approach when early experimental results were not promising. Subsequentially, the calculated bond dissociation enthalpies, along with the enthalpy of addition of a radical to styrene, have proven to be reliable indicators for the suitability of new reversible terminators.

Both AM1 and PM3 are useful in predicting the relative reactivity of reversible terminator-capped polystyrene for various capping groups. Recent experimental measurements[19] of the activation enthalpy for this reaction suggest that for nitroxides both AM1 and PM3 correctly predict the relative reactivity of nitroxides but underestimate the bond strength in these systems. PM3 performs somewhat better, underestimating the bond strength by approximately 6 kcal/mol.

Future work will focus on applying these methodologies to other systems of interest such as acrylates, methacrylates, and vinyl ethers.

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(19) Experimental enthalpies of activation for the TEMPO–styrene–BPO and 3-carboxy-PROXYL–styrene–BPO systems have been measured recently to be 130 ± 4 kJ/mol (31 kcal/mol) and 113 ± 4 kJ/mol (27 kcal/mol), respectively. The experimental values support the trend predicted by the semiempirical calculations, with the semiempirical calculations underestimating the experimental bond dissociation enthalpies by about 6 kcal/mol. Veregin, R. P. N.; Georges, M. K.; Hamer, G. K.; Kazmaier, P. M., manuscript submitted for publication.

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