How Well Can Theory Predict Addition–Fragmentation Equilibrium Constants in RAFT Polymerization?

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High level ab initio molecular orbital calculations are used to study the addition–fragmentation equilibrium constants of S-S’-bis(methyl-2-propionate)-trithiocarbonate mediated polymerization of methyl acrylate in toluene at −30 ºC. The results, which show strong solvent and chain length effects, are in good order of magnitude agreement with recent experimental results for a closely related system.

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Reversible addition–fragmentation chain transfer (RAFT) chemistry has proven to be a powerful tool in the construction of a range of complex architecture polymers with predetermined molecular weights and narrow polydispersities.[1] Control is achieved by protecting the majority of propagating species from bimolecular termination processes through their reversible trapping into a dormant thiocarbonyl compound known as a RAFT agent (see Scheme 1). Its success rests upon a delicate balance of the rates of several competing reactions, so as to ensure that the concentration of the dormant species is orders of magnitude greater than the active species and the exchange between the two forms is rapid. The design of appropriate kinetic models, and the measurement of accurate kinetic parameters for these models, can greatly assist in optimizing the process.

Unfortunately, the measurement of the rate and equilibrium coefficients of the individual reactions within a RAFT polymerization process is not straightforward as, even if potential side reactions are ignored, a ‘complete’ reaction scheme for the process may contain in excess of 100 kinetically distinct, chemically-controlled reactions, not to mention the chain-length dependent termination reactions.[2] As a result, it becomes necessary to make simplifying assumptions when fitting such models to experimental data and these assumptions can be a potential large source of error. Quantum chemistry offers a potential solution to these problems, as it allows one to study the individual reactions within a complex multi-step process directly, without recourse to kinetic model-based assumptions, other than the laws of quantum mechanics. It also provides access to important mechanistic information, such as transition state geometries and electron distributions, which are invaluable in interpreting structure-reactivity trends. However, the many-electron Schrödinger equation has no analytical solution, and in order to solve it, various numerical approximations need to be made. Although accurate methods exist, these are computationally intensive and their computational cost scales exponentially with the size of the system and thus cannot be practically applied to large polymeric molecules.

Despite these problems, in recent years ourselves[3] and others[4] have shown that accurate predictions of propagation rate coefficients in free-radical polymerization are possible through the application of high-level ab initio molecular orbital calculations to small model reactions, carefully chosen to be capable of mimicking the behaviour of their polymeric counterparts. So that these models can be as realistic as possible, we have introduced various cost-saving measures such as Energy-Directed-Tree-Search our new computationally efficient algorithm for searching conformational space,[5] and an ab initio version of the ONIOM method.[6] These procedures have not only been used to reproduce experimental values of the propagation rate coefficients in free-radical polymerization to within chemical accuracy,[3] but have also been successful in more complicated systems such as atom transfer radical polymerization (ATRP).[7] In RAFT polymerization, there have also been encouraging results. In particular, we have reproduced the experimental equilibrium constants for the addition of small radicals to thioketones.[8] We have also successfully simulated the experimental concentration profiles for the initialization of cyanoisopropyl dithiobenzoate-mediated polymerization of styrene, by combining ab initio predictions of the various addition–fragmentation equilibria with standard experimental values for the other reactions in the process.[9]

Nonetheless, despite this progress, the application of computational chemistry to radical polymerization processes remains challenging, particularly for solvent sensitive systems, and its accuracy for RAFT polymerization specifically continues to be questioned. In particular, there has been considerable...
controversy concerning the stability and fate of the intermediate RAFT-adduct radical in cumyl dithiobenzoate (CDB) mediated polymerizations, with, for example, alternative experimental estimates of the fragmentation rate for certain systems differing by six orders of magnitude.[10] Theoretical calculations, which support one of these alternative experimental estimates, indicate that these radicals are relatively stable. Whilst this is certainly consistent with several of the available experimental observations (not least the success of thiokepone mediated polymerization[10]), it is not consistent with the rate and equilibrium constants estimated from experimentally observed radical concentrations, at least within the context of the existing kinetic model for RAFT. This either implies that the theoretical calculations are flawed or that the current kinetic models, as used to interpret the experimental data, are incomplete. Indeed, a modified kinetic model that successfully reconciles all conflicting theoretical and experimental results has recently been suggested.[11] Nonetheless, further evaluation of the accuracy of the theoretical calculations, which are model independent, is important, as they can be used to evaluate alternative kinetic models, and evaluate new RAFT agents before experimentation, provided their accuracy can be established.

Recently Buback et al.[12] developed an elegant laser flash photolysis method for measuring the addition and fragmentation rate coefficients in RAFT polymerization. Although the rate coefficients obtained from this new technique are not strictly model-independent, the measurements have been shown to be insensitive to the assumed presence or absence of termination reactions involving the RAFT-adduct radical, one of the key points of contention in the CDB rate retardation controversy. Hence, data obtained from this new technique is promising for evaluating the accuracy of the theoretical calculations. Unfortunately technical issues have thus far prevented the study of the styrene/CDB system itself; however, results for the S-S′-bis(methyl-2-propionate)-trithiocarbonate (BMPT, see Scheme 2) mediated polymerization of butyl acrylate in toluene at −30°C have been reported. The aim of the present work is to use high-level ab initio molecular orbital calculations to study a model of this system, with a view to evaluating the accuracy of the theoretical data. As part of this work, we use theory to study the chain length dependence of the addition–fragmentation equilibrium, which is by necessity, ignored in the experimental study. Such information could be used to improve the kinetic models used in analyzing the experimental studies.

Standard ab initio molecular orbital theory and density functional theory calculations were performed using Gaussian 03[13] and Molpro 2006.1[14] software, using a high-level of theory, previously shown to reproduce experimental equilibrium constants for radical addition to C=S double bonds to within an order of magnitude.[8] Geometries of all species were optimized at the B3LYP/6–31G(d) level of theory and scaled frequency calculations were also performed at that level; a level previously shown to reproduce geometries and frequencies obtained via high-level

\[ \text{M}^+ + \text{S} = \text{C(SM)}_2 \rightarrow \cdot \text{C(SM)}_3 \] (1)

\[ \text{I}^+ + \text{S} = \text{C(SM)}_2 \rightarrow \cdot \text{C(SM)}_3 \text{Si} \] (2)

\[ \text{IM}^+ + \text{S} = \text{C(SM)}_2 \rightarrow \cdot \text{C(SM)}_3 \text{SM} \] (3)

\[ \text{IMM}^+ + \text{S} = \text{C(SM)}_2 \rightarrow \cdot \text{C(SM)}_3 \text{SM} \text{MM} \] (4)

\[ \text{MM}^+ + \text{S} = \text{C(SM)}_2 \rightarrow \cdot \text{C(SM)}_3 \text{SM} \text{MM} \] (5)

\[ \text{M}^+ + \text{S} = \text{C(Si)} \text{SM} \rightarrow \cdot \text{C(SM)}_3 \text{Si} \] (6)

\[ \text{M}^+ + \text{S} = \text{C(SM)} \text{SM} \rightarrow \cdot \text{C(SM)}_3 \text{SM} \] (7)

\[ \text{M}^+ + \text{S} = \text{C(SMM)} \text{SM} \rightarrow \cdot \text{C(SM)}_3 \text{SM} \text{MM} \] (8)

\[ \text{M}^+ + \text{S} = \text{C(SM)} \text{SM} \rightarrow \cdot \text{C(SM)}_3 \text{SM} \text{MM} \] (9)

\[ \text{M}^+ + \text{S} = \text{C(Si)} \text{SM} \rightarrow \cdot \text{C(SM)}_3 \text{Si} \] (10)

\[ \text{IM}^+ + \text{S} = \text{C(SM)}_2 \rightarrow \cdot \text{C(SM)}_3 \text{Si} \] (11)

\[ \text{IMM}^+ + \text{S} = \text{C(SM)}_2 \rightarrow \cdot \text{C(SM)}_3 \text{SM} \text{MM} \] (12)

\[ \text{MM}^+ + \text{S} = \text{C(SM)}_2 \rightarrow \cdot \text{C(SM)}_3 \text{SM} \text{MM} \] (13)

I indicates initiator fragment I1 or I2, M is a model of the MA propagating radical, −CH(CH₃)COOCH₃.

Scheme 3. Reactions studied.
known that the ester side chain in radical polymerization of acrylates has a relatively minor effect on propagation kinetics,[15] and is therefore also likely to have a minimal influence in the present reactions. The equilibrium constant obtained for this reaction in toluene at 243.15 K (1.4 × 10^4 L mol^-1) is within an order of magnitude agreement with experimental results (9.5 × 10^2 L mol^-1), despite the fact that the theoretical value corresponds to one individual model reaction and the experimental value is effectively a composite of the variety of possible reactions involving propagating radicals of various chain lengths in combination with initial RAFT agent and polyRAFT agents of various chain lengths.

To explore these chain length effects in more detail, we next calculated the equilibrium constants for the other reactions shown in Scheme 3 (see Fig. 1; corresponding data are provided in the Accessory Publication). These comprise the reactions of the first four possible propagating radicals (i.e. initiator fragment, monomer, dimmer, and trimer) with the initial RAFT agent, and the reactions of the model monomeric propagating radical with the first four possible RAFT agents. Since the experimental study used 2-methyl-1-[4-(methylthio)phenyl]-2-morpholinopropan-1-one (MMMP, see Scheme 2) as the initiator, two different initiator fragments were considered as chain ends for the propagating radical (see Scheme 2) in each set of reactions.

From Fig. 1, we see a very marked dependence on the equilibrium constant for the first few steps of the polymerization process, similar to that seen in our earlier studies of CDB-mediated systems.[2] This reflects the differing affinities of the two initiator fragments and the monomer-radical for the RAFT agent. These effects become much less significant as the initiator fragment becomes further removed from the radical centre. Once this fragment moves beyond the penultimate position of the chain (i.e. once the propagating radical is modelled as a dimer, with the initiator fragment in the ante-penultimate position), there is convergence to within an order of magnitude. For the RAFT agent substituent, the chain length effects show order of magnitude convergence once the initiator fragment moves beyond the terminal position of the chain. Importantly, in both cases, if the initiator fragment is removed altogether, and a simple monomeric model of the methyl acrylate propagating radical is used (as in the model Reaction 1, Scheme 3), the results obtained also show order of magnitude agreement with the trimer values, as well as with experimental values.

The consequences of these chain length effects are threefold. First, from a kinetic modelling perspective, this study re-confirms the need to take into account the strong chain length effects on the addition–fragmentation equilibrium when modelling the initialization of RAFT processes.[2] This is also clear in Fig. 2, which shows the overall free energies for chain transfer
between the various types of propagating radical and the initial RAFT agent. Whereas the propagating radicals terminated by initiator fragment I2 can exchange with the initial RAFT agent, those terminated by I1 do not exchange with the initial RAFT agent until the I1 fragment is sufficiently remote from the reaction centre. These differences in selectivity would have a significant effect on the concentration profiles of the various low molecular weight thiocarbonyl compounds formed during the early stages of this process. Second, it appears that these early chain length effects do converge quite rapidly and, provided the laser flash photolysis experiments are taken to sufficiently high molecular weights, the chain length effects should not significantly affect the measured rate coefficients, which show good agreement with the converged theoretical values. Third, from a quantum-chemical perspective, the study suggests that, while chain length effects for the first few steps are highly significant, they stem mainly from the terminal and penultimate unit effects of the initiator fragments and it may be possible to obtain good order of magnitude results for the long chain reactions using simplified monomeric models as in Reaction 1 (Scheme 3).

Finally, it is worth noting that the addition–fragmentation equilibrium constants calculated herein are significantly influenced by solvation effects. A listing of the calculated gas- and solution-phase free energies is provided in the Accessory Publication, but on average the gas-phase values are ~30 kJ mol\(^{-1}\) more exothermic (i.e. the equilibrium constants are approximately six orders of magnitude higher). Given this, it is worth re-examining our earlier gas-phase calculations of the thioketone\(^{[9]}\) and cumyl dithiobenzoate\(^{[18]}\) mediated systems, to determine whether our neglect of solvation effects compromised the accuracy of these earlier calculations. Using the same procedures as the present work, we therefore calculated the solvation free energies in toluene for \(t\)-butyl radical addition to di-\(t\)-butyl-thioketone, and cumyl radical addition to methyl dithiobenzoate at the temperatures of these earlier studies (i.e. 298.15 K and 303.15 K respectively). In each case, we find that the solvation effects are much smaller in these cases, well within the 1–2 orders of magnitude error estimated in these earlier works. Specifically, the calculated gas-phase equilibrium constant for \(t\)-butyl radical addition to di-\(t\)-butyl-thioketone\(^{[16]}\) changes from 7.9 × 10\(^5\) to 2.4 × 10\(^4\) L mol\(^{-1}\), and that for cumyl radical addition to methyl dithiobenzoate\(^{[18]}\) changes from 7.3 × 10\(^3\) to 1.6 × 10\(^2\). The reason for the stronger solvation effects in the present work is due to the greater polarity of the acrylates, and their greater potential for hydrogen bonding.

In conclusion, we have successfully used high-level \(ab\ initio\) molecular orbital calculations to study the addition–fragmentation equilibria of BMPT-mediated polymerization of methyl acrylate, as a model for the corresponding experimental data for BMPT-mediated polymerization of butyl acrylate. Our studies indicate strong early chain length effects that converge relatively rapidly to within an order of magnitude of the corresponding experimental values. These chain length effects would need to be taken into account when modelling the initialization period but their neglect is unlikely to affect the accuracy of the values measured via laser-flash photolysis. Our work also indicates strong solvation effects in these systems, several orders of magnitude greater than in the corresponding styrene/CDB system. In the present equilibrium systems, these effects are reasonably well-modelled by a simple continuum model; however, they are likely to introduce computational difficulties in kinetic calculations (as continuum model cavities are not parameterized for transition states) and also in protic solvents (where explicit solute-solvent interactions are likely to play a greater role). Notwithstanding these potential limitations, the present study re-confirms the growing potential of computational chemistry as a kinetic tool for the radical polymer field.

### Accessory Publication

Complete B3LYP/6-31G(d) optimized geometries and corresponding W1-ONIOM total energies are available on the Journal’s website.

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### References


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