**Introduction**

Methods for controlling the molecular weight and architecture in free-radical polymerization have transformed the polymer field as they combine the versatility of a radical process with the ability to generate complex macromolecular architectures such as comb, star, and block copolymers for use in bioengineering and nanotechnology applications. A variety of processes exist, including atom transfer radical polymerization (ATRP), nitroxide-mediated polymerization (NMP), and reversible addition-fragmentation chain transfer (RAFT) polymerization. Although their chemistry varies considerably, a common feature of these methods is their need to protect the majority of the growing polymer chains from the bimolecular termination reactions that normally occur in conventional free-radical polymerization. Since such radical–radical reactions are typically orders of magnitude faster than the propagation step, attempts to protect the propagating species from termination via chemically modifying its reactivity are not normally successful as they can prevent chain growth from occurring. Instead, controlled radical polymerization processes rely upon a kinetic strategy, in which the propagating species is protected from bimolecular termination through its reversible trapping as a dormant species. Their success is crucially dependent upon choosing control agents and reaction conditions that strike an optimal balance between the rates of several competing reactions, and thus there is a need to obtain reliable kinetic and mechanistic information on the rates of the individual reactions. This review highlights the practical contributions of computational quantum chemistry to our kinetic and mechanistic understanding of one such controlled radical polymerization process, the RAFT process.

In the RAFT process, control is achieved using dithioester compounds, known as RAFT agents. The propagating radical adds to the thiocarbonyl sulfur center of the dithioester to produce an intermediate carbon-centered radical. This carbon-centered radical can then undergo β-scission, either to re-form the propagating radical or to liberate a new carbon-centered radical (the ‘leaving group’).
The R group of the RAFT agent is chosen so that it undergoes $\beta$-scission from the RAFT-adduct radical in preference to the propagating species, but is still capable of reinitiating polymerization. As a result, the initial RAFT agent ($S\equiv C(Z)SR$) is rapidly converted into the polyRAFT agent, $R\cdots$ is converted into more propagating species, and eventually there is a symmetrical equilibrium as follows:

\[ \begin{align*}
    &\text{propagating radical} \\
    &\text{RAFT agent} \\
    &\text{RAFT-adduct radical} \\
    &\text{polyRAFT agent} \\
    &\text{leaving group}
\end{align*} \]

\[ \begin{align*}
    k_p \quad P_n^m \\
    S-Z-R \\
    k_{add} \quad k_{Sadd} \\
    S-Z-R \\
    k_{b} \quad k_{Sb} \\
    S-Z-R \\
    k_f \quad P_n^m
\end{align*} \]

Michelle Coote was awarded a Ph.D. in polymer chemistry from the University of New South Wales in 2000. Her Ph.D. research, which was carried under the supervision of Professor Tom Davis, used a combination of experimental and theoretical techniques to demonstrate that penultimate unit effects were significant in free radical copolymerization. The work was awarded the 2000 Cornforth Medal from the Royal Australian Chemical Institute and 2001 IUPAC Prize for Young Scientists. After postdoctoral research in polymer physics with Professor Randal Richards at the University of Durham, UK, she moved to the Research School of Chemistry, The Australian National University, to learn computational chemistry under the direction of Professor Leo Radom. She was awarded the Rita Cornforth Fellowship in 2003, and is now a fellow and group leader at the Research School of Chemistry, where she uses computational chemistry to solve practical chemical problems, particularly in the polymer field. Her recent contributions include the first chemically accurate predictions of rate coefficients in free radical polymerization, the computer-aided chemical design of a new class of multipurpose RAFT agent, and a new method for incorporating phosphorus atoms into the backbones of polyolefins. She has authored over 60 publications in the fields of computational chemistry, radical chemistry and polymer chemistry, and is a member of the ARC Centre of Excellence in Free Radical Chemistry and Biotechnology.

Ekaterina Izgorodina obtained her Ph.D. in theoretical chemistry under the supervision of Professor Stefan Grimme at the University of Muenster, Germany in 2004. During her Ph.D. she explored methods of approximating high-level ab initio methods such as coupled cluster for application to large organic molecules. The outcomes of this project included a novel energy-selective approach in coupled cluster theory and a new theoretical approach in predicting 0-0 excitation energies. After her Ph.D. she accepted a position at the Research School of Chemistry, The Australian National University, to join the computational polymer chemistry group under the direction of Dr. Michelle Coote. She is currently involved in studying chain-length dependence effects in free-radical polymerization and RAFT polymerization. Her contributions to the polymer field were the design of a new computationally efficient algorithm for finding the global minimum conformations and accurate predictions of propagation rate coefficients in free-radical polymerization.

Elizabeth Krenske was born in Brisbane, Australia. She completed her undergraduate degree at the University of Queensland, where she was a University Medallist and was named Alumni Graduate of the Year (2002). She subsequently undertook her graduate studies as a Vice-Chancellor’s scholar at The Australian National University. Her research projects have involved experimental studies of coordination chemistry, organoarsenic chemistry, and stereoselective synthesis. Since completing her Ph.D. in 2005, she has joined the computational group of Dr. Michelle Coote at the Research School of Chemistry, The Australian National University, as a postdoctoral fellow. Currently she is working on projects involved with the fundamental study of small-ring heterocycles, the control of polymerization in novel phosphorus-containing systems, and the use of phosphorus-based reagents as chain carriers in free-radical chemistry.
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, but the exchange between the two forms is rapid. The reactivity of the RAFT agent must be tailored to match the reactivity and stability of the polymeric propagating radical; information on the mechanism, kinetics, and thermodynamics of these individual steps can greatly assist in the design of optimal RAFT agents.

As in any complex multi-step process, the kinetics and thermodynamics of the individual reactions are difficult to study via experimental approaches without recourse to kinetic model-based assumptions. This is because the experimentally observable properties of the process are not the rates and equilibrium constants of the individual reactions, but rather the overall polymerization rate, the average molecular weight distribution of the resulting polymer, and the concentrations of some of the major species. In order to infer the individual rate and equilibrium constants from these measured quantities, one has to assume a kinetic scheme and often make additional simplifying assumptions (such as the steady-state assumption). This problem is exacerbated in controlled radical polymerization processes such as RAFT because there are too many reactions that are potentially kinetically distinct and should thus be considered in a complete kinetic model of the process. For example, even assuming that the addition-fragmentation equilibria are chain-length independent beyond the dimer radical stage, one would still have to consider the reactions of seven different types of radical (initiator fragment 1•, leaving group R, unimer and dimer radicals each having I or R as their chain end, and the macroradical). Each of these radicals could be transferred to the RAFT agent, giving rise to seven different types of dithioester compound, each of which could react with the seven types of radical (see Scheme 1). In other words, there could be potentially 49 (kinetically distinct) addition reactions and 49 fragmentation reactions to consider in a ’complete’ model of the process. These are in addition to the various reinitiation reactions and the usual initiation, propagation, termination, and transfer reactions. Since it is impractical to fit a model with 100 or more adjustable parameters to the experimental data, simplifications are necessary; for example, most published studies have replaced the 98 potential addition-fragmentation parameters with just two or four. Whilst some such simplifications are probably justifiable under certain circumstances, they can also be a potentially large source of systematic error. For example, depending upon the type of data measured and the associated model-based assumptions used, alternative experimental values for the equilibrium constant in the cumyl dithiobenzoate (CDB)-mediated polymerization of styrene at 60 °C differ by six orders of magnitude.\[6,7\]

Computational quantum chemistry offers an attractive solution to this problem, as it allows the individual reactions to be studied without recourse to kinetic model-based assumptions. Using \textit{ab initio} molecular orbital theory, it is possible to predict the kinetics and thermodynamics of chemical reactions from first principles, assuming only the laws of quantum mechanics and a few fundamental physical constants (such as the masses and charges of the electron, proton, and neutron). Moreover, such calculations yield a range of additional properties such as the geometries and vibrational frequencies of the reactants, products, and transition structures, and the distribution of charge and spin density within them. Indeed, as noted by Paul Dirac in 1929, ‘the underlying physical laws necessary for the mathematical theory of a large part of physics and the whole of chemistry are thus completely known, and the difficulty is only that the exact application of these laws leads to equations much too complicated to be soluble.’\[8\] Therein also lies the problem: since there is no analytical solution to the many electron Schrödinger equation, various numerical simplifications and approximations must be made. A variety of methods exist, differing principally in the size of their basis set and their treatment of electron correlation. The most accurate methods reliably deliver ‘sub-kcal accuracy’ but require enormous computational resources, their computational cost scaling exponentially with the size of the system; cheaper methods can be used to study much larger systems but are much less reliable.

To apply quantum-chemical methods to reactions of relevance for free-radical polymerization processes necessarily involves a compromise in which, on the one hand, the most computationally efficient methods are selected that still deliver acceptable accuracy, and, on the other, small model systems are designed that still mimic the kinetic behavior of the polymeric reactions. Recently, it has been shown that a successful compromise is now possible for the prediction of propagation rate coefficients in free-radical polymerization\[9\] and, on the basis of extensive assessment studies\[9–14\] a methodological approach that delivers ‘chemical accuracy’ for a variety of radical reactions including radical addition to dithioester compounds has been designed. Already, computational calculations have helped to provide an insight into structure-reactivity patterns in RAFT polymerization,\[6,11,15–20\] and have led to the design of a new class of RAFT agent.\[21,22\] Moreover, computational chemistry is also making a contribution to our understanding of other controlled radical polymerization processes, such as ATRP\[19,23,24\] and NMP\[25,26\] as well as conventional radical polymerization.\[27–38\] With continuing advances in computer power, more applications are anticipated and computational chemistry will take its place alongside experimental methods as a practical kinetic tool.

In the present work, the use of quantum chemistry to study the RAFT polymerization process is reviewed. It begins with a description of the types of methods that are used, and their accuracy and their outstanding problems are discussed. The contributions that computational chemistry
Scheme 1.

[1] R- + ZC[^S]_R → R[^S]C[^S]_R
[2] I- + ZC[^S]_R → R[^S]C[^S]_R
[8] I- + ZC[^S]_I → I[^S]C[^S]_I
[9] I-M[^S]_I + ZC[^S]_I → I[^S]C[^S]_I
[19] I-M[^S]_M + ZC[^S]_M_I → I[^S]C[^S]_M_I

has made to clarifying and improving models for reaction kinetics, modeling and explaining structure-reactivity trends, and designing new and improved RAFT agents are then outlined.

**Methodology**

In order to select reliable yet cost-effective theoretical procedures, assessment studies are performed. In essence one takes a small prototypical example of the class of chemical reactions under study, and calculates the geometries, frequencies, barriers, enthalpies, rate coefficients, and other properties at a variety of levels of theory, ranging from the extremely accurate but highly computationally intensive down to those that are computationally inexpensive but potentially subject to very large errors. For each type of property, one compares the results at the lower levels of theory with the highest-level results and (where possible) also with reliable gas-phase experimental data. For the case of addition-fragmentation processes, assessment studies have been performed for the prototypical reactions $\text{CH}_2 + S = \text{C}(\text{R})\text{R}' 
\rightarrow \text{CH}_2\text{SC}(\text{R})\text{R}'$ ($\text{R}' = \text{H}, \text{CH}_3$)$^{[10]}$ and also the more RAFT-related systems, $R'S\text{C}(Z) = S + R' \rightarrow R'S\text{C}(Z)\text{S}R$ (various combinations of $R, R' = \text{CH}_3, \text{CH}_2\text{CH}_3, \text{CH}_2\text{CN}, \text{C}(\text{CH}_3)\text{CN}, \text{CH}_2\text{COOHCH}_3, \text{CH}(\text{CH}_3)\text{- COOHCH}_3, \text{CH}_2\text{OCHCH}_3, \text{CH}_2\text{Ph}, \text{CH}(\text{CH}_3)\text{Ph}$, and $Z = \text{CH}_3, \text{H}, \text{Cl}, \text{CN}, \text{CF}_3, \text{NH}_2, \text{Ph}, \text{CH}_2\text{Ph}, \text{OCH}_3, \text{OCH}_2\text{CH}_3, \text{OCH}(\text{CH}_3)_2, \text{OC}(\text{CH}_3)_3, \text{F})^{[12]}$. In addition, the accuracy of the harmonic oscillator approximation$^{[11,17]}$ and the applicability of standard (rather than variational) transition state theory have been explored.$^{[11]}$ On the basis of these studies, the following guidelines for performing theoretical calculations are suggested.

**Electronic-Structure Calculations**

In general, it is possible to conduct reliable geometry optimizations and frequency calculations for the stationary species (i.e., the reactants and products) in the RAFT process at relatively low levels of theory, such as B3-LYP/6-31G(d) or HF/6-31G(d).$^{[10]}$ For example, provided the energies are calculated at a consistent level of theory, the reaction enthalpies for $\text{CH}_3 + S = \text{CRR}'$ ($\text{R}', \text{R}'' = \text{H}, \text{CH}_3$) vary by less than 1 kJ mol$^{-1}$, regardless of whether low levels such as B3-LYP/6-31G(d) or HF/6-31G(d) or higher levels such as CCSD(T)/6-311+G(d,p) are used for the geometry optimizations.$^{[10]}$ Likewise, provided the recommended scale factors are used,$^{[39]}$ the zero-point vibrational energy (and hence the frequency calculations) at these lower levels of theory agrees to within 1–2 kJ mol$^{-1}$ of the CCSD(T)/6-311+G(d,p) calculations.$^{[10]}$ However, for transition structures, extra precautions are required. In particular, density functional theory (DFT) methods such as B3-LYP significantly overestimate the length of the forming bond in the transition state, finding transition structures that are too early. HF fares somewhat better, but does underestimate the forming bond length, finding transition structures that are too late. To address this problem, the transition structures should be corrected to higher levels of theory via IRCmax.$^{[10]}$ In the IRCmax method,$^{[40,41]}$ one calculates the minimum energy path of the chemical reaction at a low level of theory, and then calculates single point energies along this reaction path at a higher level of theory, such as RMP2/6-311+G(3df,2p). The IRCmax transition structure is then identified as that species corresponding to the maximum point of the minimum energy path, as calculated at the higher level of theory. In essence, one optimizes the most sensitive part of the geometry optimization (i.e., the reaction coordinate) at the higher level of theory, at a fraction of the cost of a full geometry optimization at that level. For the case of radical addition to C=S bonds, the IRCmax transition structures have bond lengths within less than 0.05 Å, and provide reaction barriers within 1 kJ mol$^{-1}$, of those obtained using full geometry optimizations at the CCSD(T)/6-311+G(d,p) level.$^{[10]}$

In contrast to geometries and frequencies, accurate calculations of the energetics of these types of chemical reactions require very high levels of theory. Ideally, such calculations should be performed using W1 theory or better. W1 aims to approximate coupled cluster energies [URCCSD(T)] with an infinite basis set via extrapolation, and includes corrections for core correlation and relativistic effects.$^{[42]}$ It has been shown to deliver ‘kJ accuracy’ when assessed against a large test set of gas-phase experimental data.$^{[42]}$ and has performed well in assessment studies for the prototypical system $\text{CH}_3 + S = \text{CH}_2$ as well as other types of radical reaction such as radical addition to C=C bonds$^{[13]}$ and hydrogen atom abstraction.$^{[14]}$ Unfortunately, such calculations are very computationally intensive and currently only practicable for up to approximately five non-hydrogen atoms. The G3 family of methods provides a lower-cost alternative to W1. Like W1, they attempt to approximate coupled cluster energies with a large basis set, but achieve this via additivity approximations at the MP2 and/or MP4 levels of theory. As a result, they are less expensive than W1 but also less reliable. They have been shown to deliver ‘kcal accuracy’ when assessed against a large test set of experimental thermochemical data$^{[43,44]}$ and to provide good agreement with W1 for a variety of radical reactions.$^{[13,14]}$ For the specific problem of radical addition to C=S double bonds, the G3 methods provide excellent agreement with W1 for the reaction barriers: for reaction enthalpies, the errors are slightly larger (ca. 10 kJ mol$^{-1}$) but are likely to be reasonably systematic for a class of reactions and, therefore, suitable for studying substituent effects.$^{[10]}$ Nonetheless, they are also currently too computationally intensive for all but the simplest RAFT systems, being currently only feasible for systems of up to approximately 17 non-hydrogen atoms.
For practical RAFT systems, lower-cost procedures are necessary and, unfortunately, these procedures can be subject to large errors. In particular, current DFT methods fail comprehensively to model the effects of substituents in addition-fragmentation processes.\(^{[12]}\) Moreover, this failing has also been observed for carbon–carbon bond energies,\(^{[45]}\) homolytic and heterolytic bond dissociation reactions,\(^{[46,47]}\) and propagation rate coefficients,\(^{[9]}\) and appears to be a general problem. Restricted open-shell second-order Møller-Plesset perturbation theory (RMP2), which is slightly more expensive than DFT but can still be practically applied to relatively large systems, has been shown to fare much better than DFT. It generally provides reasonable absolute values (within 10 kJ mol\(^{-1}\)) and excellent relative values (within 4 kJ mol\(^{-1}\) or better) for the barriers and enthalpies of the addition-fragmentation processes\(^{[10,12]}\) as well as a variety of other radical reactions.\(^{[9,13,14,46,47]}\) However, it breaks down when the attacking radical is substituted with a group (such as phenyl or CN) that delocalizes the unpaired electron, with errors of over 15 kJ mol\(^{-1}\) being reported in some cases.\(^{[11,12]}\) Since such radicals are common in practical RAFT systems, this severely compromises the utility of RMP2.

Given these problems, an alternative approach has been designed that is based on the ONIOM procedure\(^{[48]}\) of Morokuma. In the ONIOM method, one first defines a ‘core’ section of the reaction that, in the very least, contains all forming and breaking bonds and would preferably include the principal substituents attached to them. In forming the core system, deleted substituents are replaced with ‘link atoms’ (typically hydrogens), chosen so that the core system provides a good chemical model of the reaction center. One then calculates the core system at both a high level of theory and also a lower level; the ‘full system’ is calculated at only the lower level. The full system at the high level of theory is then approximated as the sum of a) the core system at the high level and b) the substituent effect measured at the low level of theory. The approximation is valid if the low level of theory measures the substituent effect accurately; this in turn depends upon the level of theory chosen, and the way in which in the core system is defined.

For the RAFT systems, it is known from the above that W1 provides accurate absolute values of barriers and enthalpies, and G3(MP2)-RAD provides excellent relative values. For small systems, such as Reaction (3), the W1 enthalpy could thus be approximated as the sum of the W1 enthalpy for the core Reaction (4), and the difference in the G3(MP2)-RAD enthalpies for Reactions (3) and (4).

\[
\text{CH}_2\text{Ph} + S = C(CH_3)SCH_3 \rightarrow \text{PhCH}_2\text{SC} \cdot (CH_3)SCH_3 \quad (3)
\]

\[
\text{CH}_3 + S = CH_2 \rightarrow \text{CH}_3\text{SCH}_2 \cdot \quad (4)
\]

For larger systems, where G3(MP2)-RAD calculations are not currently feasible, an additional ‘ONIOM-layer’ is added in which the full system is calculated using RMP2/6-311+G(3df,2p), the core system is calculated using G3(MP2)-RAD, and the ‘inner core’ is studied at W1. For example, one could approximate the W1 enthalpy for Reaction (5) as the sum of the W1 value for the inner core (4), the G3(MP2)-RAD difference for the core (3) and inner core (4), and the RMP2/6-311+G(3df,2p) difference for the full (5) and core (3) systems.

\[
\text{CH}((\text{Ph})\text{CH}_2\text{C}(\text{CH}_3)_2\text{CN} + S = C(\text{CH}_2\text{Ph})SC(\text{CH}_3)_2\text{Ph} \rightarrow (\text{CH}_3)_2\text{C}(\text{CN})\text{CH}_2\text{CH}(\text{Ph})\text{SC} \cdot (\text{CH}_2\text{Ph})SC(\text{CH}_3)_2\text{Ph}
\]

(5)

The ONIOM procedure provides an accurate alternative to high-level calculations on the full system, provided that the lower level of theory measures the substituent effects accurately. While the RMP2/6-311+G(3df,2p) method normally provides excellent relative values of barriers and enthalpies, it does break down in situations where the unpaired electron is highly delocalized. It is, therefore, extremely important to partition the full and core systems carefully, such that the delocalized radical is treated at the G3(MP2)-RAD level of theory and the RMP2/6-311+G(3df,2p) method is used only to measure remote substituent effects. Based on a careful assessment study, the following general guidelines are suggested\(^{[12]}\) for partitioning the core and full systems: in the addition-fragmentation Reaction (6), a suitable core system should include all \(\alpha\)-substituents on the attacking radical \(R\) but could replace the \(R'\) group with a methyl substituent and, if necessary, also replace the \(Z\) group with a methyl substituent.

\[
R + S = C(Z)SR' \rightarrow \text{RSC} \cdot (Z)SR' \quad (6)
\]

Even when the \(Z\) group is itself a substituent capable of delocalizing the unpaired electron in the RAFT-adduct radical, its replacement with \(CH_3\) in the core system does not introduce substantial error.\(^{[12]}\) This is presumably because the radical is already highly delocalized by the thiyl groups (which are of course included in both the core and inner core systems), and the additional delocalization by the phenyl substituent is not as significant as in an ordinary carbon-centered radical.\(^{[18]}\) This ONIOM-based procedure allows one to study quite large RAFT systems (ca. 30–40 non-hydrogen atoms) with kcal accuracy.\(^{[12]}\) Similar performance has also been demonstrated for propagation\(^{[9]}\) and radical ring-opening.\(^{[49]}\)

Kinetics and Thermodynamics

Having obtained the geometries, energies and frequencies of the reactants, products, and transition structures, it is possible to calculate the rates \(k(T)\) and equilibrium
constants \(K(T)\) of chemical reactions, using the standard
textbook formulae,\(^{[50,51]}\)

\[
k(T) = \kappa(T) \frac{k_B T}{h} (c^e)^{1-m} e^{(-\Delta G^+/RT)}
\]

\[
= \kappa(T) \frac{k_B T}{h} (c^e)^{1-m} \frac{Q^i}{\Pi_{Q_j \text{reactants}}} e^{(-\Delta E^i/RT)}
\]

(7)

\[
K(T) = (c^e)^{\Delta m} e^{(-\Delta G/RT)} = (c^e)^{\Delta m} \left( \prod_{\text{products}} Q_j \right) \prod_{\text{reactants}} Q_i e^{(-\Delta E/RT)}
\]

(8)

In these formulae, \(\kappa(T)\) is the tunneling correction factor,
\(T\) is the temperature (K), \(k_B\) is Boltzmann’s constant
\((1.380658 \times 10^{-23} \text{ J \cdot mole}^{-1} \cdot \text{K}^{-1})\), \(h\) is Planck’s
constant \((6.6260755 \times 10^{-34} \text{ J \cdot s})\), \(c^e\) is the standard unit
of concentration \((\text{mol} \cdot \text{L}^{-1})\), \(R\) is the universal gas constant
\((8.3142 \text{ J \cdot mol}^{-1} \cdot \text{K}^{-1})\), \(m\) is the molecularity of the
reaction, and \(\Delta n\) is the change in moles upon reaction. \(Q_i\) and \(Q_j\) are the molecular partition functions of the transition
structure, reactant \(i\) and product \(j\) respectively, \(\Delta G^i\) is the
Gibbs free energy of activation, \(\Delta G\) is the Gibbs free energy
of reaction, \(\Delta E^i\) is the 0 K, zero-point energy corrected
energy barrier for the reaction, and \(\Delta E\) is the 0 K, zero-point
energy corrected energy change for the reaction. The value of \(c^e\) depends on the standard-state concentration assumed in
calculating the thermodynamic quantities (and translational
partition function). For example, if these quantities
were calculated for 1 mole of an ideal gas at 333.15 K and
1 atm, then \(c^e = P/RT = 0.0365971 \text{ mol} \cdot \text{L}^{-1}\). The tunneling
coefficient \(\kappa(T)\) corrects for quantum effects in motion along
the reaction path.\(^{[52–55]}\) Whilst tunneling is important in
important in certain chemical reactions, such as hydrogen abstraction,
it is negligible (i.e., \(\kappa \approx 1\)) for the addition of carbon-
centered radicals to thiocarbonyl compounds at typical
polymerization temperatures (such as 333.15 K) because
the masses of the rearranging atoms are large and the
barriers for the reactions are relatively broad.\(^{[11]}\)

The molecular partition functions and their associated
thermodynamic functions (i.e., enthalpy, \(H\), and entropy, \(S\)) can be calculated using the standard textbook formulae,\(^{[50,51]}\) based on the statistical thermodynamics of an
ideal gas under the harmonic oscillator/rigid rotor approximation.
These formulae require knowledge of the point
group, multiplicity, geometry, and vibrational frequencies of each species: the accuracy of the results depends upon
both the accuracy of the calculated geometries and frequencies
and also the validity of the harmonic oscillator/rigid rotor
approximation. As noted above, the geometries and frequencies are well described at relatively low levels of theory,
such as B3-LYP/6-31G(d), provided that transition
structures are corrected via IRCmax and frequencies are
scaled by appropriate scale factors. However, the use of the
harmonic oscillator/rigid rotor approximation can lead to
errors of 1–2 orders of magnitude in both the kinetics and
thermodynamics of the addition-fragmentation equili-
trium.\(^{[11,17]}\) To address this problem, the partition functions
for the low frequency torsional modes (<300 cm\(^{-1}\)) should
instead be treated as hindered internal rotations. Full details
of these calculations are published elsewhere,\(^{[11]}\) but a short
description is provided below.

For each low frequency torsional mode, one first calculates
the full rotational potential \(V(\theta)\). This can be calculated at a relatively low level of theory, such as B3-
LYP/6-31G(d), and is performed as a relaxed (rather than
frozen) scan in steps of 10° through 360°. The potential is
then fitted with a Fourier series of up to 18 terms, so that it
can be interpolated to a finer numerical grid (typically 300
points instead of 36).

The corresponding energy levels are found by numerically solving the one-dimensional Schrödinger Equa-
tion (9) for a rigid rotor.\(^{[28,56,57]}\)

\[
-\frac{\hbar^2}{8\pi^2 I} \frac{\partial^2 \Psi}{\partial \theta^2} + V(\theta) \Psi = \epsilon \Psi
\]

(9)

The reduced moment of inertia (\(I\)) is calculated using the equation for \(I^{2,3}\), as defined by East and Radom.\(^{[58]}\)

The resulting energy levels \(\epsilon_i\) are then summed to obtain the
partition function at the specified temperature, as follows:

\[
Q_{\text{int rot}} = \frac{1}{\sigma_{\text{int}}} \sum_i \exp\left(-\frac{\epsilon_i}{k_B T}\right)
\]

(10)

where \(\sigma_{\text{int}}\) is the symmetry number associated with that
rotation. It should be noted that, in this method, the low
frequency torsional modes have been approximated as one-
dimensional rigid rotors, while in practice these modes
are coupled with another. However, a recent study of coupled
internal rotations in another radical addition reaction (ethyl
benzyl radical addition to ethene) indicate that the errors
incurred in using a one-dimensional treatment are relatively
minor, particularly when compared with the errors incurred
under the harmonic oscillator approximation.\(^{[59]}\)

In evaluating the rate coefficients, the method for identifying
the transition structure is also important. Standard
gometry optimization algorithms identify the transition
structure as a first-order saddle point in the potential energy
surface: that is, as the structure having the maximum internal
energy (\(E\)) along the minimum energy path. However,
ideally the rate calculations should be performed using the
structure having the maximum Gibbs free energy (\(G\)). At
non-zero temperatures, \(E\) and \(G\) are non-equal and thus the
gometries corresponding to their maximum values are not
necessarily equivalent. The corresponding methods for
calculating the rate coefficients are known as standard
transition state theory and variational transition state
theory, respectively.\(^{[60]}\) Variational transition state theory is
more accurate but also more expensive, as it entails the
calculation of the energies and partition functions at not just

the transition structure but at several points along the minimum energy path. In practice, for reactions with significant energy barriers, the differences between transition state theory and variational transition state theory are relatively minor, and the lower-cost standard method can be used. However, for barrierless reactions (or for some low barrier reactions), variational effects can become important.

Radical addition to the sulfur atom of a C=S double bond is typically a fast reaction, having a low or even negative barrier (ΔE°) in most cases. The positive Gibbs free energy barrier results from opposing enthalpic and entropic effects.\[^{[11]}\] In other words, both ΔE and ΔH decrease along the reaction coordinate but −TΔS increases and its opposing interaction leads to the maximum in ΔG. Under these circumstances, one might have expected variational effects to be very important for these systems. However, in a recent assessment study for the prototypical RAFT systems RCH=CH(S)-C(R=CH₃, CH₂Ph, CH₂COOCH₃, C(CH₃)₂CN; Z=CH₃, Ph, CH₂Ph) it is found that, provided the transition structures are corrected via IRCmax, the use of variational transition state theory has little or no effect on the reaction barriers.\[^{[11]}\] The effects on the entropies and hence reaction rates are somewhat larger (up to a factor of 16) in the case of the CH₃ addition reactions, but for the reaction of the substituted radicals (which are more indicative of real polymerization systems), they remain relatively small (ca. a factor of 2). Thus, while variational transition state theory should always be used when possible for these systems, standard transition state theory may be adopted for large systems without incurring significant additional error.

### Solvent Effects

The methodology described thus far is designed to reproduce chemically accurate values of the rate and equilibrium constants for gas-phase systems; however, the majority of RAFT polymerizations occur in solution. The development of cost-effective methods for treating the solvent in chemical reactions is an ongoing area of research\[^{[61,62]}\] and there have not yet been any benchmark studies for the specific case of RAFT polymerization. However, it is worth making a few general comments on the types of solvent models that are currently available. The simplest and most computationally efficient methods are continuum models, in which each solute molecule is embedded in a cavity surrounded by a dielectric continuum of permittivity ε.\[^{[62]}\] Some of the more sophisticated continuum models, such as the ab initio conductor-like solvation model (COSMO)\[^{[63]}\] and the polarizable continuum model (PCM),\[^{[64]}\] also include terms for the non-electrostatic contributions of the solvent, such as dispersion, repulsion, and cavitation. Continuum models are designed to reproduce bulk or macroscopic behavior, and can fare extremely well in certain applications such as the calculation of the solvation free energies\[^{[65]}\] and pKₐ values\[^{[66]}\] of various organic molecules. However, the results obtained using continuum models are highly sensitive to the choice of cavities (which are typically parameterized to reproduce the free energies of solvation for a set of small organic molecules), and the choice of appropriate cavities for weakly bound species such as transition structures can be problematic.\[^{[65]}\] Moreover, their description of important electronic effects is not generally adequate, particularly if there are explicit solute-solvent interactions such as complex formation and hydrogen bonding. Although this problem can be overcome by including a small number of explicit solvent molecules in the ab initio calculation, as in a cluster-continuum model,\[^{[67]}\] this adds significantly to the cost of the calculation. Such explicit solute–solvent interactions might be expected to be particularly important when studying aqueous-phase polymerizations and monomers capable of undergoing strong hydrogen-bonding interactions (such as acrylic acid).

Of greater concern for the study of the kinetics and thermodynamics of association and dissociation processes (as in RAFT), is the fact that continuum models completely ignore the changes to the (ideal gas) vibrational, translational, and rotational partition functions upon solvation.\[^{[68]}\] In the gas phase, the reactants and products have translational and rotational entropy, whereas in the solution phase this entropy is effectively ‘lost’ in collisions with the solvent. In place of the translational and rotational motion, the solution-phase molecules have additional internal degrees of freedom corresponding to their interaction with the solvent. However, these additional modes generally contribute less to the total entropy of a molecule than the corresponding external translational and rotational modes in the gas phase. The difference between the gas-phase and solution-phase entropy is significant in a bimolecular association reaction (i.e., A + B → C), because three translational and three rotational modes are converted into internal modes on reaction. Since these lost modes contribute less to the total entropy in the solution phase, the solution-phase reaction is expected to be less exothermic than the corresponding gas-phase reaction, and thus it should have a larger equilibrium constant and a faster rate coefficient. Clear evidence for this ‘entropic’ solvent effect can be found in comparisons of corresponding experimental gas-phase and solution-phase rate coefficients for radical addition to alkenes. In these cases, the solution-phase rate coefficients generally exceed the gas-phase values by an order of magnitude.\[^{[69]}\]

Unfortunately, there is no straightforward manner in which to quantify these entropic contributions to the solvent effect. Normally, one must include many explicit solvent molecules in the calculation and try to reproduce bulk behavior via molecular dynamics or Monte Carlo simulations, combined with the imposition of periodic boundary conditions.\[^{[70]}\] Such calculations are hampered by problems such as the lack of potentials that can adequately describe...
both cluster and bulk behavior and the rapid increase in
the conformational possibilities as number of individual
components increases. Nonetheless there is a growing body
of work towards addressing these problems. In particular,
the effective fragment potential method, in which the Col-
umbic, induction, and repulsive interactions are included as
one-electron terms in the \textit{ab initio} Hamiltonian, is showing
promise as an accurate yet cost-effective method for
developing potentials for any solute-solvent combina-
tion.\cite{71} There is also some progress toward the ultimate
goal of formulating a dynamical correction to gas-phase
transition state theory rate coefficients.\cite{61,72} An examina-
tion of the accuracy and applicability of the various solvent
models for radical reactions such as RAFT is currently
underway, but until general guidelines for the accurate
treatment of solvent effects are derived, gas-phase calcu-
lations are preferred. With the exception of systems
displaying strong direct interactions, it is expected that
the neglect of the solvent will not introduce substantial
erors to the trends in the calculated rates and equilibrium
constants, but may affect the absolute values. In particular,
as noted above, the use of gas-phase calculations may lead
to an underestimation of the solution-phase values of the
rate and equilibrium constants for bimolecular association
reactions by at least an order of magnitude.

\textbf{Accuracy and Outstanding Challenges}

Normally, one might establish the accuracy of \textit{ab initio}
calculations through comparison with reliable experimen-
tal data. However, in the case of the RAFT process this is
difficult as there is no model-free manner in which to
measure experimentally the rates and equilibrium constants
of the individual addition-fragmentation processes. As
explained above, even if one makes the assumption that
addition and fragmentation are chain length independent
beyond the dimer stage, a complete kinetic model would
need to contain in excess of 100 adjustable parameters. As a
result, various simplifications and approximations are made
in obtaining experimental measurements, and these are a
potential source of error. Alternative experimental meas-
urements for ostensibly the same system can differ by
several orders of magnitude, and choosing the ‘correct’
experimental value for comparison with the theoretical data
is problematic. For example, although there is excellent
agreement between the calculated equilibrium constant of
$27$ and the experimental value of $7.3 \times 10^6$ L mol$^{-1}$ for CDB-
mediated polymerization of styrene at 303.15 K and the
experimental values of $1.06 \times 10^7$ L mol$^{-1}$ obtained
from model-fitting to low-conversion kinetic data,\cite{60} both
the experimental and theoretical values are in conflict
with those estimated from electron paramagnetic reso-
nance (EPR) data but under different polymerization
conditions.\cite{75}

Given this problem, other strategies for testing the accu-
curacy of the theoretical calculations have been used instead.
To begin with, we recall that the levels of theory have been
selected on the basis of assessment studies, and their
accuracy established through comparison with high levels
of theory, themselves benchmarked against gas-phase
thermochemical data.\cite{10–12} On the basis of these assess-
ment studies, it is concluded that the selected procedures
can model the absolute barriers and enthalpies for the
radical addition of C=O double bonds to within 1 kcal.
mol$^{-1}$. It is also possible to benchmark the calculations
against (relatively model-free) solution-phase experimental
data for related small systems. For example, Scaino and
Ingold\cite{73} have studied the addition of \textit{t}-\textit{t}-\textit{t}er\textit{t}-\textit{t}-butyl radicals to
di-\textit{t}-\textit{t}-\textit{t}er\textit{t}-\textit{t}-butyl thioacetate via laser flash photolysis to obtain
an equilibrium constant of $1.2 \times 10^6$ L mol$^{-1}$ at 25 °C.
This is in very good agreement with the corresponding
theoretical value ($7.9 \times 10^6$ L mol$^{-1}$),\cite{74} the latter being
slightly lower because of the neglect of the solvent in the
calculations. The computational methodology can also be
compared with experimental data for polymeric systems for
the case of the propagation rate coefficients. Although not
chemically identical to an addition-fragmentation reaction,
a propagation reaction is still a radical addition reaction and
has the advantage that reliable experimental data can be
obtained using pulsed laser polymerization (PLP).\cite{75} A
recent computational study of the propagation of vinyl
chloride and acrylonitrile yielded values within a factor of 2
of the experimental polymeric values, and demonstrated
that the rate coefficient for the polymeric propagating
species was adequately modeled using the corresponding
rate coefficient for the dimer.\cite{59} Further studies of a wider
range of monomers are currently underway, but it does seem
that ‘chemical accuracy’ is now attainable.

Despite this success, a number of challenges remain. In
particular, as noted above, the treatment of solvent effects is
not yet satisfactory, and larger errors might be expected for
solvent-sensitive systems such as acrylic acids. It should
also be stressed that the above methodology is not suitable
for studying the diffusion-controlled termination processes.
In principle one could calculate the chemically controlled
component of the termination reaction using computational
chemistry, and this could be extremely helpful in some
situations. For example, there is currently a debate about
whether the RAFT-adduct radical is capable of undergoing
termination,\cite{6,7,76–84} to establish whether the chemically
controlled component is fast or slow would be an impor-
tant contribution to this debate. However, the above
methodology, which makes use of methods with single-
reference wavefunctions, is not likely to be suitable for
studying the transition structure of a radical–radical
process. Unfortunately, multireference methods are con-
siderably more computationally intensive and further work
is needed to identify reliable low-cost alternatives for such
systems.
Even in the case of the addition-fragmentation reaction, the computational cost of the calculations remains an issue. Although the ONIOM-based approach facilitates the calculation of accurate energetics for relatively large systems, other computational bottlenecks are now emerging. Larger systems (such as the reactions of dimer radicals with RAFT agents) have a high degree of conformational complexity, and finding the minimum energy conformations of these species can be very computationally demanding. Currently these are identified via a complete conformational search: that is, the geometries are optimized for every (non-unique) conformation about every bond (or forming bond) in the molecule (or transition structure). For example, in a relatively simple species such as \((\text{CH}_3)_2\text{C(Ph)}-\text{CH}_2-\text{CH(Ph)}-\text{S-C(Ph)}-\text{S-C(CH}_3)_2\text{Ph})\), 324 possible conformations may need to be considered. Inserting just one extra styryl unit increases the number of possible conformers to 2916 and the calculations rapidly become impractical. A more efficient algorithm for exploring conformational space is currently being investigated.[85] Preliminary indications are that it is possible to find the global minimum reliably at the cost of approximately 10% of a full search, but further savings would be desirable. A related computational bottleneck stems from the need to treat the low frequency torsional modes as hindered internal rotations. As explained above, this entails the calculation of full rotational potentials (typically 36 geometry optimizations) for each mode considered. This too can rapidly become computationally infeasible, and strategies for reducing this computational expense are currently being investigated. Nonetheless, despite these problems, it is now possible to perform accurate calculations on systems that are large enough (ca. 30–40 non-hydrogen atoms) to be of relevance to practical polymerization systems.

Computational Modeling of RAFT Kinetics

One of the main advantages of a computational approach to studying RAFT polymerization kinetics is the ability to determine the rate and equilibrium constants of individual reactions directly, without having to fit a kinetic model to data. This is particularly useful for complex processes such as RAFT because the kinetic models for these processes potentially can contain more adjustable parameters than can practically be estimated from the available experimental data. For example, as noted earlier, even if the assumption is made that the addition-fragmentation equilibrium becomes chain length independent beyond the dimer stage, a ‘complete’ kinetic model for the process would need to contain 49 addition rate coefficients and 49 fragmentation rate coefficients (see Scheme 1), in addition to various reinitiation rate coefficients, and the usual initiation, propagation, termination, and transfer coefficients. Since this is impractical, experimental studies typically make simplifying assumptions - such as replacing all 98 rate coefficients by just 2 or 4 - and these are a potential source of error. In particular, such simplifications are likely to affect the description of subtle yet important effects such as the concentration profiles of the various species during the early stages of the process.[86,87]

Computational chemistry can assist the kinetic modeling of RAFT in a number of ways. Firstly, it is possible to study the effects of chain length and other remote substituents on the addition-fragmentation equilibria. This information can be used to identify which simplifying assumptions are justifiable in a kinetic model, and thereby assist experimental studies. The same information can also be used to assist the computational studies by identifying which substituents can be replaced with smaller groups without affecting the calculated results. Secondly, it is possible to use computational chemistry to establish whether side reactions (such as alternative fragmentation pathways) are likely to be operative in particular systems, and thus whether they need to be taken into account in the kinetic modeling schemes. Finally, it is possible to calculate the rate and equilibrium constants for many of the early reactions in the RAFT process, and thereby help to minimize the number of adjustable parameters that need to be measured experimentally. Indeed, provided suitable small models for the polymeric reactions can be designed, it is possible in principle to calculate all chemically controlled rate coefficients for a RAFT process, so as to evaluate the performance of new RAFT agents prior to experimental studies. These aspects are now reviewed in turn.

Simplified Models for Theory and Experiment

Both theoretical and experimental studies of radical polymerization processes rely heavily on the fact that, in a chemically controlled reaction, the effects of substituents diminish rapidly with their distance from the reaction center. From an experimental perspective, it allows one to treat the reactions of species differing only in their remote substituents as identical, thereby reducing the number of adjustable parameters in kinetic models. From a theoretical perspective, it allows one to replace these unimportant remote substituents with smaller chemical groups, thereby reducing the computational cost of the calculations. For example, in free-radical copolymerization, the reactivity of the propagating radical is determined solely by the nature of its terminal and penultimate units, and is independent of the chemical composition of the remainder of the polymer chain.[88] As a result, kinetic models for copolymerization need only to consider the propagation reactions of four

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*One would need to use experimental data for the diffusion controlled termination rate coefficients but these could be obtained from a single homopolymerization polymerization of the specified monomer in the absence of RAFT agent.*
types of propagating radical instead of thousands, while computational studies can determine the radical and monomer reactivity ratios using dimers as chemical models of the propagating species. This has been confirmed in both experimental\(^{[89,90]}\) and theoretical\(^{[99]}\) studies of the homopropagation rate coefficients, which indicate that the rate coefficients have largely converged to their long chain limit at the dimer radical stage and have completely converged well before the decamer stage.

In the RAFT process, there are two key areas where simplifications to kinetic and theoretical studies are desirable. In the generic addition-fragmentation process \(\text{R}^\bullet + \text{S} = \text{C}(Z)\text{SR}'\), it is important to discover whether the kinetics and thermodynamics are affected by the nature of the ‘attacking group’ (\(\text{R}^\bullet\)) and the ‘non-participating group’ (\(\text{R}'\)) and, if so, at what point the remote substituent effects become negligible. Recent experimental\(^{[3,91,92]}\) and theoretical\(^{[11,17–19,93,94]}\) studies of the effects of substituents on the RAFT process indicate that the kinetics and thermodynamics are extremely sensitive to the nature of the attacking radical and the Z group of the RAFT agent (\(\text{S} = \text{C}(Z)\text{SR}'\)). For example, the equilibrium constant (at 333.15 K) for \(\text{CH}_3\) addition to \(\text{S} = \text{C}(\text{CH}_3)\text{SCH}_3\) increases by approximately six orders of magnitude when the \(\text{CH}_3\) Z group is replaced with a phenyl substituent, and decreases by seven orders of magnitude when the methyl attacking group is replaced with the \(2,2'\)-azoisobutyronitrile (AIBN) fragment, \(\text{C}(\text{CH}_3)_2\text{CN}\).\(^{[17]}\) It is, therefore, essential that reactions that differ in the nature of their Z groups and/or the primary substituents of their R groups are treated as being kinetically distinct. The influence of the \(\text{R}'\) is less significant and some simplifications are possible. For example, the calculated equilibrium constants for \(\text{CH}_3\) addition to \(\text{S} = \text{C}(\text{CH}_3)\text{SR}'\) for \(\text{R}' = \text{CH}_2\text{X}, \text{CH}(\text{CH}_3)\text{X}, \text{and C}(\text{CH}_3)_2\text{X}\) and \(\text{X} = \text{H}, \text{CH}_3, \text{CN}, \text{Ph}, \text{COOCH}_3, \text{and COOCH}_3\) range over three orders of magnitude (see Table 1).\(^{[93]}\) However, this effect is mainly steric in origin, the bulky \(\text{R}''\) groups destabilize the thiocarbonyl compound to a greater extent than the more flexible RAFT-adduct radical. As a result, the \(K\) values for individual classes of mono-substituted, di-substituted, and tri-substituted \(\text{R}'\) groups fall into much smaller ranges and, depending on the nature of the monomer and initial \(\text{R}'\) group, it may be possible to ignore the effect of \(\text{R}'\) in some kinetic models.

Given that the \(\text{R}, \text{Z}, \text{and}, \text{to some extent, \(\text{R}'\) groups all affect the addition-fragmentation equilibrium, it is not surprising that the addition-fragmentation equilibrium is also affected by the chain length of the \(\text{R}\) and \(\text{R}'\) groups. Figure 1 shows the effects of chain length \((n)\) on the equilibrium constants for the addition of styryl radicals of varying chain length \((\text{NC}(\text{CH}_3)_2–(\text{CH}_2\text{CHPh})_n\text{)} (n = 0, 1, 2, 3)\) to \(\text{S} = \text{C}(\text{Ph})\text{SCH}_3\), and the addition of \(\text{CH}_3\) radicals to the corresponding poly-RAFT agents, \(\text{S} = \text{C}(\text{Ph})\text{S}–(\text{CHPhCH}_2)_{n–1}\text{C}(\text{CH}_3)_2\text{CN}\).\(^{[93]}\) The \(-\text{C}(\text{CH}_3)_2\text{CN}\) end-group that is imparted by the initiating species, when AIBN is used as the initiator. It should be noted that, in the case of the trimer species, this end group is omitted entirely, owing to the large computational cost of the calculations. Not surprisingly, the equilibrium constants change by several orders of magnitude when the first monomer unit is inserted into the respective chains, as the primary substituents on the respective \(\text{R}\) and \(\text{R}'\) groups are altered. In the case of the attacking radical (i.e., the \(\text{R}\) group), the equilibrium constants continue to change as successive styryl units are inserted into the chain. Thus, from Figure 1 it is seen that the equilibrium constant increases by a factor of 73 when the first styryl unit is inserted, it increases by a further factor of 672 when the second unit is inserted, but increases by less than a factor of 4 when the third unit is inserted. Since the end group was omitted in calculating the latter species, it is possible that when the full trimer is investigated larger deviations will be observed, but the indications are that reasonable convergence occurs at the trimer stage. In the case of the RAFT agent substituent (i.e., the \(\text{R}'\) group), the chain length effects are much smaller but are nonetheless significant. Insertion of the first styryl unit causes the equilibrium constant to decrease by a factor of 67, while insertion of the second causes an increase by a factor of 10. Calculations of the full trimer species are again required in order to establish convergence, but the H-terminated trimer species converges to within a factor of 3.

### Table 1. Effect of \(\text{R}'\) on the calculated enthalpies \((\Delta H)\), entropies \((\Delta S)\), and equilibrium constants \((K)\)\(^{[93]}\) at 333.15 K for the model RAFT reaction, \(\text{CH}_3 + \text{S} = \text{C}(\text{CH}_3)\text{SR}' \rightarrow \text{CH}_3\text{SC} (\text{CH}_3)\text{SR}'\).

<table>
<thead>
<tr>
<th>(\text{R}')</th>
<th>(\Delta H) (kJ \cdot mol(^{-1}))</th>
<th>(\Delta S) (J \cdot mol(^{-1}) \cdot K(^{-1}))</th>
<th>(K) (L \cdot mol(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{CH}_2\text{X})</td>
<td>76.0</td>
<td>149.0</td>
<td>3.8 \times 10^7</td>
</tr>
<tr>
<td>(\text{CH}_3\text{X})</td>
<td>79.9</td>
<td>138.6</td>
<td>1.8 \times 10^7</td>
</tr>
<tr>
<td>(\text{CH}_3\text{X})</td>
<td>92.9</td>
<td>161.5</td>
<td>1.8 \times 10^7</td>
</tr>
<tr>
<td>(\text{CN})</td>
<td>87.8</td>
<td>166.4</td>
<td>1.5 \times 10^7</td>
</tr>
<tr>
<td>(\text{COOCH}_3)</td>
<td>90.0</td>
<td>168.1</td>
<td>3.3 \times 10^7</td>
</tr>
<tr>
<td>(\text{COOCH}_3)</td>
<td>92.0</td>
<td>166.3</td>
<td>1.8 \times 10^7</td>
</tr>
</tbody>
</table>

\(^{[93]}\) \(\Delta H\) (kJ \cdot mol\(^{-1}\)), \(\Delta S\) (J \cdot mol\(^{-1}\) \cdot K\(^{-1}\)), and \(K\) (L \cdot mol\(^{-1}\)) calculated at the W1-ONIOM/B3-LYP/6-31G(d) level of theory in conjunction with the harmonic oscillator approximation and taken from ref.\(^{[93]}\).

In summary, it is clear that in the early stages of the reaction, chain-length effects in the attacking radical, and to a lesser extent the RAFT agent substituent, are significant and their neglect leads a serious over-simplification of the initialization kinetics. Based on the currently available computational results, it seems reasonable to suppose that reactions of the various primary species (R• and 1•), unimolecular radicals (I–M• and R–M•), dimeric radicals (R–M–M and I–M–M•), and longer chain species do need to be treated as being kinetically distinct. It is also possible that chain length effects beyond the trimer position are also important, and it is also possible that for certain systems chain length effects are smaller than in the case of styrene polymerization. For highly accurate results, the RAFT agents derived from each of these should also be treated as being kinetically distinct, though the chain length effects in these cases are much smaller. Nonetheless a ‘complete’ kinetic model of the addition-fragmentation kinetics would thus resemble that provided in Scheme 1, and would contain far too many unknown parameters for fitting to experimental data alone. Computational chemistry offers the prospect of reducing the number of unknown parameters by providing direct calculations of the relevant values for the early small-molecule reactions of the RAFT process, leaving experiment to estimate a smaller number of parameters corresponding to the longer chain radicals.

**Side Reactions**

In designing an appropriate kinetic model for RAFT polymerization, it is also necessary to determine whether additional side reactions need to be incorporated into the kinetic scheme. In principle, one could use computational chemistry to find all possible side-reactions of a process from first principles. However, this would entail the calculation of a complete multi-dimensional potential energy surface for the chemical system, followed by molecular dynamics simulations for a wide variety of possible trajectories. Unfortunately, this is currently too computationally intensive for practical RAFT systems. However, it is possible to study specific postulated side reactions and test whether they are likely to occur. For example, if hydrogen abstraction reactions involving the RAFT-adduct radical were suspected to be a problem in certain polymerization systems, one could calculate rate coefficients for the various possible reactions (i.e., abstraction of the different hydrogen atoms on the monomer, polymer, RAFT agent, and so forth). By comparing their rates with the normal β-scission reaction, one could thereby establish which (if any) of the possible abstraction reactions were likely to be competitive.

To date only one type of side reaction has been identified computationally. In this work, computational chemistry is used to study the competitive β-scission of the C–O bond of the alkoxy group in xanthate-mediated polymerization of vinyl acetate. Rate coefficients (333.15 K) for both the normal β-scission of the vinyl acetate radical and the side reaction are calculated for a series of model RAFT-adduct radicals, CH2SC(OZ)SCH2OCOCH3 for Z′ = Me, Et, i-Pr and t-Bu (see Scheme 2). It is shown that for the Z′ = Me, Et, and i-Pr systems, the normal β-scission reaction is favored and this is consistent with the experimental observation that these systems display normal RAFT behavior. In contrast, for the t-Bu case, the side reaction is preferred, and this provides a suitable explanation for the experimentally observed inhibition in this system. In general, it would be worth considering this side reaction when the Z′ substituent of the xanthate is a good radical leaving group (such as t-Bu) and/or the propagating radical is a poor leaving group (as in vinyl acetate or ethylene polymerization).

Other side reactions might also be conceivable under certain circumstances, though their feasibility is yet to be examined computationally. As noted above, there is some debate as to whether the RAFT-adduct radical is capable of undergoing irreversible and/or reversible termination reactions (see Scheme 3) to any significant extent in normal polymerizing RAFT systems. Although computational quantum chemistry is not currently capable of predicting diffusion-controlled rate coefficients, computational calculations could nonetheless be used to calculate the chemically controlled component of the termination rate and establish a lower boundary to the termination rate coefficient. To this end, work is currently underway to...
identify cost-effective multireference methods for studying such systems. Another side reaction that is worth considering is the attack of the propagating radical at the carbon center (rather than the sulfur center) of the C=S bond to produce a sulfur-centered radical. Studies of radical addition to simple thiocarbonyl compounds indicate that this side reaction is actually thermodynamically preferred, though it is kinetically less favorable by 1–2 orders of magnitude.\[^{10,96}\] This is attributable in part to the greater steric hindrance at the carbon center and in part to the stronger early bonding interaction when attack occurs at sulfur (see below).\[^{96}\] In RAFT systems, the steric hindrance at the carbon center is yet greater, and the kinetic preference for addition at carbon should normally be very small. Nonetheless, given that addition to the RAFT agent occurs many thousands of times during the lifetime of the propagating radical, even a low relative rate of addition at carbon might be sufficient to affect the polymerization kinetics in certain systems. Other side reactions that have been suggested include reaction of the RAFT-adduct radical with monomer (i.e., copolymerization), and reactions with oxygen impurities.\[^{3}\] Computational calculations of these and other pathways could help to establish their feasibility and clarify their mechanism.

**Computational Model Predictions**

Provided calculations are performed at an appropriately high level of theory, computational chemistry can be used to determine the rates and equilibrium constants for the individual reactions in a RAFT polymerization. The resulting values can then be used to study structure-reactivity trends, reduce the number of adjustable parameters in a kinetic analysis of experimental data, or, ultimately, predict the kinetic behavior of a RAFT polymerization system from first principles. Table 2 shows a compilation of the main equilibrium constants that have been reported to date. Owing to their greater computational expense, the rate coefficients have been reported for a number of small model systems and these are provided in Table 3. Where necessary, the rates and equilibrium constants have been improved to the W1-ONIOM level of theory and recalculated at a consistent temperature (333.15 K). Values obtained under harmonic oscillator approximation are reported for all systems and where possible the more accurate hindered rotor values are also reported.

The data confirm that the equilibrium constants (and thus the addition-fragmentation kinetics) are very dependent upon the nature of the attacking radical and the RAFT agent. In a practical RAFT system it is not valid to treat all of the possible reactions as having the same rates. Thus, for example, when calculated at a uniform level of theory, the equilibrium constants for the addition of a styryl radical to RAFT agents of the form S=CH(Ph)S(CH(CH\(_3\))\(_2\)) vary from 2.9 × 10\(^5\) to 3.6 × 10\(^9\), depending on whether styryl is modeled as a unimer with an H end group, a C(CH\(_3\))\(_2\)CN end group, a C(CH\(_3\))\(_2\)Ph end group, or as a dimer with an H end group. This explains why simplified models do not appear to be capable of describing the initialization period in RAFT systems, and may help to explain the large discrepancies in the experimental values for the rates and equilibrium constants in CDB-mediated polymerization that are obtained by fitting simplified models to experimental data.

Secondly, although the equilibrium constants vary considerably, this variability arises mainly in the fragmentation reaction. For most substituents, the addition rate coefficients fall into a relatively narrow range (10\(^5\)–10\(^7\) L mol\(^{-1}\) s\(^{-1}\)). In these cases, it may be reasonable to treat all (or most) of the possible addition reactions in a specific process as having the same rate coefficients, provided the rates of their reverse fragmentation reactions are allowed to vary. However, there are a few important exceptions. In particular, the addition of propagating radicals to xanthates

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**Scheme 2.**

<table>
<thead>
<tr>
<th>(Z^*)</th>
<th>(k_\text{p, alkoxy})</th>
<th>(k_\text{p, normal})</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>3.2 × 10(^4)</td>
<td>2.3 × 10(^5)</td>
<td>1.4 × 10(^{-1})</td>
</tr>
<tr>
<td>Et</td>
<td>3.5</td>
<td>1.7 × 10(^5)</td>
<td>1.2 × 10(^{-5})</td>
</tr>
<tr>
<td>(\beta)-Pr</td>
<td>1.6 × 10(^2)</td>
<td>6.8 × 10(^2)</td>
<td>2.4 × 10(^{-1})</td>
</tr>
<tr>
<td>(t)-Bu</td>
<td>2.1 × 10(^5)</td>
<td>1.7 × 10(^2)</td>
<td>1.2 × 10(^3)</td>
</tr>
</tbody>
</table>
is typically much slower than to dithioesters (Z = alkyl, aryl) unless the propagating radical is highly reactive (as in vinyl acetate polymerization). As a result of their slow addition rate, monomers with stable propagating radicals (such as styrene) are not normally well controlled by xanthates. Moreover, within the xanthate reactions themselves, there is a large variation in the addition rate coefficient depending whether the propagating radical is capable of undergoing H-bonding interactions with the alkoxy group of xanthate in the transition structure (see below). Indeed, this H-bonding interaction may be partially responsible for the success of xanthates in controlling vinyl acetate. In this regard, it is worth noting that the xanthates have been less successful in controlling ethylene polymerization, another system in which the propagating radical is relatively unstable but for which the H-bonding interaction is absent. From Table 3, it is seen that, even for the methyl radical, which might reasonably be expected to be more reactive than the ethyl propagating species, the addition rate coefficient for the xanthate agent is relatively low (ca. $10^4$ L·mol$^{-1}$·s$^{-1}$).

Finally, the data indicate that slow fragmentation of the RAFT-adduct radical can help to explain the experimentally observed inhibition periods in CDB-mediated polymerizations.$^{[6]}$ Kinetic studies$^{[97]}$ indicate that rate retardation is likely to be significant when $K$ is greater than or equal to approximately $10^6$ L·mol$^{-1}$. The equilibrium constants for the addition of unimers of methyl acrylate ($3.6 \times 10^7$) and dimers ($3.6 \times 10^9$) of styrene satisfy this condition, while that for the addition of cumyl ($2.5 \times 10^5$) and the styrene unimer ($6.6 \times 10^5$) lie within the level of possible error. In contrast, fragmentation of C(CH$_3$)$_2$CN from the RAFT-adduct radical is not predicted to be retarded ($7.4 \times 10^4$), which is consistent with the experimental observation$^{[98]}$ that cyanoisopropyl dithiobenzoate does not display a significant inhibition period. On the basis of Table 2, other retarded processes would include the fragmentation reactions of the RAFT-adduct radicals bearing a cyano Z group, and the fragmentation of ethyl radicals and vinyl acetate radicals from the adduct radicals of dithioesters. Table 2 also correctly predicts that in the case of vinyl acetate this rate retardation is relieved when xanthates are

---

**Scheme 3.**

---

[Diagram of Scheme 3]
Table 2. Effect of R, Z, and R’ on the calculated equilibrium constants ($K_a$) at 333.15 K for the model RAFT reaction, $\bullet R + S = C(Z)SR' \rightarrow RSC(Z)SR'$. 

<table>
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<tr>
<th>$R^*$</th>
<th>Z</th>
<th>$R'$</th>
<th>$K$ (HO)</th>
<th>$K$ (HR)</th>
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(Continued)
Table 2. (Continued)

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<th>R’</th>
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<th>K (HR)</th>
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<tr>
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</tbody>
</table>

Equilibrium constants K (L·mol⁻¹) calculated at the W1-ONIOM/B3-LYP/6-31G(d) level of theory in conjunction with the harmonic oscillator approximation (HO) and, where data were available, also the hindered rotor model (HR). The original electronic structure data were taken from previous studies[6,12,16–18,21,22,93,94,110] and corrected to the W1-ONIOM level in the present work using W1 calculations[10] for the core reaction. For most systems a two-layer ONIOM approach was possible in which the inner core was calculated at W1 and the rest of the system at G3(MP2)-RAD. For a limited number of larger systems (such as reactions in which Z = Ph and reactions of dimer radicals with various substrates), a three-layer ONIOM approach was used in which the outer layer was calculated at RMP2/6-311+G(3df,2p).

Structure-Reactivity Studies

Another area where computational quantum chemistry has an important role to play is in providing an underlying reactivity trends. At one level, computational chemistry can be used as a tool for determining the rate or equilibrium constants of the individual addition-fragmentation processes for a variety of RAFT agent and monomer combinations. In this regard, it offers a complementary approach to experimental techniques, which are better suited to measuring more practical quantities, such as the extent of control or the apparent chain transfer constant. At a deeper level, computational chemistry can also offer convenient access to additional mechanistic information, such as the geometries, charges, and spin densities, and to other relevant

Table 3. Calculated addition (k_{add}), fragmentation (k_{frag}), and equilibrium (K) constants at 333.15 K for the model RAFT reaction, \( \cdot R + S=\text{C}(Z)\text{CH}_3 \rightarrow RSC\text{C}(Z)\text{CH}_3 \).

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<th>Z</th>
<th>k_{add} (HO)</th>
<th>k_{add} (HR)</th>
<th>k_{frag} (HO)</th>
<th>k_{frag} (HR)</th>
<th>K (HO)</th>
<th>K (HR)</th>
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<td>OCH₃</td>
<td>3.9 × 10⁶</td>
<td>5.0 × 10⁷</td>
<td>3.0 × 10⁶</td>
<td>1.3 × 10⁹</td>
<td>1.5 × 10⁻⁴</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rate coefficients for addition (L·mol⁻¹·s⁻¹) and fragmentation (s⁻¹) and equilibrium constants (L·mol⁻¹) calculated at the W1-ONIOM/B3-LYP/6-31G(d) level of theory in conjunction with the harmonic oscillator approximation (HO) and, where data were available, also the hindered rotor model (HR). The original electronic structure data were taken from previous studies[11,15,16,110] and corrected to the W1-ONIOM level in the present work using W1 calculations[10] for the core reaction. Reactions of the CH₃ and CH₂OOCCH₃ radical with the xanthates were studied via standard transition state theory; all other reactions were studied via variational transition state theory.
energetic quantities, such as radical stabilization energies of the adduct radical. This information can greatly assist in the interpretation of the structure-reactivity trends. Based on both \textit{ab initio} calculations and experimental approaches, there is now a very good understanding of why C=S double bonds are so effective at addition-fragmentation reactions, and how the RAFT agent substituents affect this process. In what follows, these fundamental and practical aspects are summarized in turn, and we then show how this information can be used to design optimal RAFT agents.

\textbf{Fundamental Aspects}

A key aspect to controlling free radical polymerization by RAFT is the establishment of an addition-fragmentation equilibrium in which there is rapid exchange between the propagating species and dormant polyRAFT agent. This in turn entails that \textit{both} the addition of the propagating radical to the RAFT agent and the fragmentation of the resulting RAFT-adduct radical (which is effectively the reverse reaction) are sufficiently fast. In radical addition to C=C bonds this is normally quite difficult to achieve. Typically, if addition is fast, the reaction is highly exothermic and fragmentation is too slow. If instead the addition reaction is not very exothermic, then fragmentation becomes relatively facile and addition is too slow. Although some success has been achieved with macromonomers,\cite{99} alkenes are not generally suitable as practical RAFT agents. The question then arises, why are compounds containing C=S bonds so much more effective, and are there any other types of double bond that would serve the same purpose?

To understand the high reactivity of thiocarbonyl RAFT agents, it is helpful to examine a simple curve-crossing model analysis of prototypical radical additions to C=S and C=C bonds.\cite{96} The curve-crossing model was developed by Pross and Shaik\cite{100–102} as a theoretical framework for explaining barrier formation in chemical reactions. The basic idea is to think of a chemical reaction as comprising a rearrangement of electrons, accompanied by a rearrangement of nuclei (i.e., a geometric rearrangement). We can then imagine holding the arrangement of electrons constant in its initial configuration (which we call the reactant configuration), and examining how the energy changes as a function of the geometry. Likewise, we could hold the electronic configuration constant in its final form (the product configuration), and again examine the variation in energy as a function of the geometry. If these two curves (energy versus geometry) are plotted, a ‘state correlation diagram’ is formed. The overall energy profile for the reaction, which is also plotted, is formed by the resonance interaction between the reactant and product configurations (and any other low-lying configurations). State correlation diagrams allow for a qualitative explanation for how variations in the relative energies of the alternative valence bond (VB) configurations affect the barrier height.

In radical addition to double bonds (X=Y), the principal VB configurations that may contribute to the ground-state wavefunction are the four lowest doublet configurations of the three-electron-three-center system formed by the initially unpaired electron at the radical carbon (R) and the electron pair of the \pi bond in X=Y (A).\cite{69}

\begin{equation}
\begin{array}{c}
\text{R}^+\text{A}^- \\
\text{R}^-\text{A}^+ \\
\text{RA}^3 \\
\text{RA} \\
\end{array}
\end{equation}

The first configuration (RA) corresponds to the arrangement of electrons in the reactants, the second to that of the products (RA$^3$), and the latter two (R$^+\text{A}^-$ and R$^-\text{A}^+$) to possible charge-transfer configurations. The state correlation diagram showing (qualitatively) how the energies of these configurations should vary as a function of the reaction coordinate is provided in Figure 2. In plotting this figure the R$^+\text{A}^-$ configuration has been arbitrarily designated to be lower in energy than the R$^-\text{A}^+$ configuration.

In the early stages of the reaction, the reactant configuration (RA) is the lowest-energy configuration and dominates the reaction profile. This is a result of the stabilizing influence of the bonding interaction in the \pi bond of the RA configuration, which is an antibonding interaction in the RA$^3$ configuration. However, as the reaction proceeds, the

![State correlation diagram for radical addition to double bonds.](image-url)
C ··· X=Y distance decreases and the unpaired electron on the radical is able to interact with the X=Y species. This growing interaction destabilizes the RA configuration but stabilizes the RA³ configuration because of the increasing bonding interaction in the forming C ··· X bond (which is an antibonding interaction in the RA configuration). As the relative energies of the RA and RA³ configurations converge, the increasing interaction between the alternative configurations stabilizes the ground state wavefunction, with the strength of the stabilizing interaction increasing as the energy difference between the alternate configurations decreases. It is this mixing of the reactant and product configurations that leads to the avoided crossing, and accounts for barrier formation. Beyond the transition structure, the product configuration is lower in energy and dominates the wavefunction. The charge-transfer configurations of the isolated reactants and the isolated products are high in energy, but in the vicinity of the transition structure they are stabilized via favorable Coulombic interactions and can sometimes be sufficiently low in energy to interact with the ground state wavefunction. In those cases, the transition structure is further stabilized, and (if one of the charge transfer configurations is lower than the other) the mixing is reflected in a degree of partial charge transfer between the reactants.

Using this state-correlation diagram, in conjunction with simple VB arguments, the curve-crossing model can be used to predict the qualitative influence of various energy parameters on the reaction barrier. In particular, the barrier is lowered by: an increase in the reaction exothermicity (see Figure 3a), and/or a decrease in the RA–RA³ separation in the reactants and/or products (see Figure 3b), and/or a decrease in the relative energies of one or both of the charge-transfer configurations, provided that these are sufficiently low in energy to contribute to the ground-state wavefunction (see Figure 3c). Of these parameters, the reaction exothermicity is of course directly accessible from ab initio molecular orbital calculations. For the radical addition reactions, the RA–RA³ separation is related to the singlet-triplet excitation gap of the alkene or thiocarbonyl species. The relative importance of the charge-transfer configurations can be assessed on the basis of the energy for charge transfer between the isolated reactants, and can be further assessed by examining the actual extent of charge transfer in the transition structures.

With these simple principles in hand, it then becomes obvious why thiocarbonyls make much more effective RAFT agents than alkenes. As is well known, the π bond of a thiocarbonyl is much weaker than that of an alkene, because of the poorer overlap between the p–π orbitals of the (third row) S atom and the (second row) C atom. This reduced π bond strength is reflected in a greatly reduced singlet-triplet gap for the thiocarbonyl species, and hence in lower barriers and earlier transition structures for radical addition. Indeed, unless there is substantial stabilization of the C=S bond (via, for example, resonance with lone pair donor substituents at carbon), radical addition to C=S bonds is typically barrierless (i.e., ΔHf ≈ 0), the free energy barrier (i.e., ΔGf > 0) arising merely as a result of opposing enthalpic and entropic effects. Conversely, in the reverse direction, the transition state is very late and almost completely dominated by the reaction exothermicity (i.e., ΔHf ≈ ΔH).

The low singlet-triplet gap not only explains why dithioesters are generally very reactive to radical addition, it also explains how it is possible to manipulate the RAFT agent substituents so as to ensure that fragmentation is also sufficiently fast. The curve-crossing model predicts that the barrier is affected by the reaction enthalpy: the less exothermic the reaction, the greater the barrier. Indeed, in the absence of any additional factors (such as steric or polar effects), the well-known Evans-Polanyi rule \( \Delta H^2 = \Delta x \Delta H \) will hold. In radical addition to C=C bonds, this raises a problem. If one wishes to promote the fragmentation reaction, one needs to make the addition reaction less exothermic but, in doing so, this raises the barrier to radical addition. In radical addition to C=S bonds this is also the case, but there is an important difference. Because of the early transition structures, the influence of the exothermicity on the addition reaction is greatly reduced (i.e., the proportionality constant \( x \) is much smaller), and there is much greater scope for manipulating the reverse fragmentation reaction without compromising the addition rate.

The dominant influence of the triplet configuration of the π bond also helps to explain the regioselectivity of the radical addition reaction. As explained above, radical addition to the carbon-center of the C=S bond is actually the thermodynamically preferred reaction, though in practice addition occurs at S because of kinetic factors. The spin density is considerably greater on S than on C in the triplet configuration of the thiocarbonyl, and there is thus a much stronger early bonding interaction when addition occurs at this site. Although the preference for

![Figure 3](image-url)
attack at sulfur is countered by the reduced exothermicity, the early transition structure ensures that influence of the triplet configuration dominates.

Finally, it is worth exploring whether compounds containing other types of double bonds would be suitable in RAFT processes. In particular, dithiophosphinate esters have been proposed as possible alternative RAFT agents. In such systems, 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.

$$
M^*P^* + S^*R^*S^*R \rightleftharpoons P^*S^*R^*S^*R \rightleftharpoons S^*R^*S^*P^* + R^* \quad (12)
$$

Although there is some experimental indication that styrene polymerization can be controlled using $S^*=P(\text{SCH- (CH$_3$)$_2$Ph})$ and $S^*=P(\text{Ph})_2\text{SCH( CH$_3$)$_2$Ph}$, the observed control is by no means perfect and there is clear evidence of hybrid behavior. Computationally, it has been shown that radical addition to the $P=S$ bonds of dithiophosphinate esters is considerably less reactive and less exothermic than addition to corresponding $C=S$ compounds. This is attributable in part to the lower inherent stabilization energy of its phosphoranyl radical product and in part to its stronger double bond. Indeed, unlike the $C=S$ double bond of dithioesters, the $P=S$ bond has a significant ionic character (i.e., a large resonance contribution from $P^+=S^-$), which generally renders it less susceptible to radical addition (unless the attacking radical is highly electrophilic). On this basis it is concluded that dithiophosphinate esters are likely to have only limited applicability as RAFT agents, and would be most suited to the control of electrophilic monomers.

The suitability of other types of compounds has yet to be explored computationally: however, studies of prototypical systems have revealed that $C=C$, $C=O$, and $C=S$ bonds all have significantly larger singlet-triplet gaps than the corresponding $C=S$ bonds. As a result they are less reactive to radical addition than $C=S$ bonds, and are less likely to function as effective RAFT agents.

**Structure-Reactivity in Practical RAFT Systems**

Notwithstanding the high reactivity of $C=S$ bonds, the precise nature of the other substituents ($R$ and $Z$) in a RAFT agent $S=C(Z)SR$ is critical to a controlled polymerization. The degree of control that can be achieved is reliant on the propensity for addition of the propagating radical $P^*$ to the $C=S$ bond, and the subsequent ability of $P^*$ to be released from the RAFT-adduct radical. Both of these depend on the steric and electronic properties of $R$ and $Z$. As a result of numerous experimental studies, there now exists a broad understanding of how effective a given $R$ or $Z$ group is for a certain class of polymerization. For example, polymerizations of styrene, acrylates, or methacrylates are well controlled by dithioester RAFT agents having simple alkyl or aryl $Z$ groups, whereas the polymerization of vinyl acetate is not. For vinyl acetate, control can be achieved with xanthates ($Z=\text{OR}$) or dithiocarbamates ($Z=\text{NR}_2$). Equally, it is known that a RAFT agent having $R=\text{benzyl}$ would be suitable for polymerization of methyl acrylate, but not for the polymerization of methyl methacrylate: the tertiary $R$ group $C(\text{CH$_3$)$_2$Ph}$ is necessary in the latter case.

Building on the wealth of structure-reactivity data now available from experimental studies, computational chemistry adds a powerful tool that allows these trends to be explained, and this in turn has predictive power. Our computational investigations have been founded on the observation that, despite the mechanistic complexity of RAFT polymerization, the effects of $R$ and $Z$ can in large part be understood by considering simplified versions of the chain-transfer Reaction (13).

$$
P^* + S^*C^*SR \rightleftharpoons P^*S^*C^*SR \rightleftharpoons P^*S^*C^* + R^* \quad (13)
$$

To begin with, it is clear from Table 3 that, as expected on the basis of the considerations detailed in the previous section, the fragmentation rate constants generally follow the same order as the fragmentation enthalpies. A useful analysis of structure-reactivity relationships can, therefore, be carried out on the basis of the thermodynamic parameters. Moreover, the analysis can be further simplified through the use of isodesmic reactions to separate and rank the effects of $R$ and $Z$. First of all, the fragmentation efficiency associated with a particular $Z$ group is measured by the enthalpy change ($\Delta H_{\text{frag}}$) for the reaction $\text{CH}_3\text{SC}(Z)\text{SCH}_3 + S^*=C(\text{H})\text{SCH}_3 \rightarrow \text{CH}_3\text{SC}(\text{H})\text{SCH}_3 + S^*=C(Z)\text{SCH}_3$. Next, the chain-transfer efficiency for a given $R$ group is measured by the enthalpy change ($\Delta H_{\text{CT}}$) for the reaction $\text{CH}_3\text{S}^* + S^*=C(\text{CH}_3)\text{SR} \rightarrow S^*=C(\text{CH}_3)\text{SCH}_3 + \text{R}^*$. The stabilities of RAFT agents with different $Z$ groups are compared by considering the enthalpies of the reactions $S^*=C(Z)\text{SCH}_3 + \text{CH}_4 \rightarrow S^*=C(\text{H})\text{SCH}_3 + \text{CH}_4$, while the stabilities of RAFT agents with different $R$ groups are compared by the reactions $S^*=C(\text{CH}_3)\text{SR} + \text{CH}_4\text{SH} \rightarrow S^*=C(\text{CH}_3)\text{SCH}_3 + \text{RSH}$. The well-known quantity, the radical stabilization energy (RSE), used to estimate the stabilities of the radical species.
In the overall chain-transfer reaction, Reaction (13), the effect of Z involves both the RAFT agent (and the polyRAFT agent) and the intermediate RAFT-adduct radical. One must therefore consider each addition-fragmentation step separately. In Figure 4, a variety of Z groups are ranked in order of increasing fragmentation efficiency $\Delta H_{\text{frag}}$. Shown on the same graph, are the stabilities of the two relevant Z-containing species: the RAFT agent and the RAFT-adduct radical. The fragmentation efficiencies span a range of 100 kJ mol$^{-1}$, making it clear that the choice of Z is critical. It has been suggested$^{[94]}$ that in considering the effects of Z, RAFT agents may be divided into three broad classes based on their values of $\Delta H_{\text{frag}}$. In one class are the agents with Z groups favoring fragmentation ($Z = \text{OR}$ or $\text{NR}_2$), in the second are those with low fragmentation efficiencies ($Z = \text{CN}$, $\text{Ph}$, or $\text{CF}_3$), and in the third are those with moderate efficiencies ($Z = \text{SR}$, and modified OR or $\text{NR}_2$). As will be discussed below, the different classes are of varying utility depending on the monomer of interest.

For the RAFT agents (and polyRAFT agents), there are two main ways in which Z affects stability. First, lone-pair donor Z groups such as OR, NR$_2$, and SR enhance stability through delocalization of electron density into the C=S bond as shown by Reaction (14).

Second, RAFT agents are destabilized by $\sigma$-withdrawal. This property can be clearly seen with the RAFT agents that have $Z = \text{CN}$ or $\text{CF}_3$. Within this stability scheme, the positions of several Z groups are worthy of note. For example, the groups $Z = \text{pyrrole}$ and imidazole confer much less stabilization on a RAFT agent than do aliphatic amino groups such as $\text{NMe}_2$. This is consistent with the notion$^{[109]}$ that incorporating the nitrogen lone pair into an aromatic system reduces the capacity for electron delocalization according to Reaction (14).

For RAFT-adduct radicals, the effects of Z are somewhat more complicated. Here, a major increase in stability is gained if Z is a $\pi$-acceptor group such as CN or Ph. Stabilization by $\pi$-acceptor groups is common for carbon-centered radicals, and in RAFT-adduct radicals the effect can be enhanced because the lone-pair donor SR groups can engage in captodative effects. In principle, the presence of a lone-pair donor Z group should be an alternative stabilizing feature (as in other carbon-centered radicals), but in RAFT-adduct radicals this is not always borne out. It has been shown$^{[18]}$ that the delocalization of electron density from an SR group onto a carbon radical center places the unpaired electron into a higher-energy orbital, making further delocalization onto a second SR group much less favorable.

A RAFT-adduct radical has two lone-pair donor SR groups.
even before Z is considered, and the capacity for a third interaction involving a lone-pair donor Z group is therefore small. Only when Z is a stronger lone-pair donor than SR will there be enhanced stabilization. Making the situation more complicated, RAFT-adduct radicals are strongly destabilized by σ-withdrawal (as demonstrated when Z = F), which means that only those Z groups for which lone-pair donation is stronger than σ-withdrawal (and stronger than the lone-pair donation by an SR group) will confer enhanced stabilization. In Figure 4, the only Z groups that satisfy both criteria are the simple amino groups NR2 (R = H, Me, Et). The alkoxy groups, although being strong lone-pair donors, are unable to enhance stability, because of their strong σ-withdrawing character.

Considering next the effects of R, we have found that it is usually sufficient to consider the overall chain-transfer equilibrium without giving separate attention to the individual steps. Several earlier computational studies have also adopted this approach. For example, semi-empirical methods have been used to show that the chain-transfer efficiency of dithiobenzoate RAFT agents varied with R in the order CH2COOEt < CH2COOH < CH(Me)COOEt.[20] A related study[19] of a wide range of R groups using DFT reached similar conclusions, and suggested that chain transfer is affected by both steric and polar effects. The overall chain-transfer equilibrium is, of course, a competition between the radicals R• and Pn• for adding to the C=S bond. In most cases, the position of the equilibrium is determined mainly by the relative stabilities of the radicals R• and Pn•: the group whose release from the RAFT-adduct radical is favored is the one whose RSE is greatest. The values of ΔHCT for a range of common R groups are shown in order of increasing chain-transfer propensity in Figure 5, together with the stabilities of the relevant RAFT agents and radicals R•.

Considering first the R• radicals, the RSEs can be largely explained on the basis of factors normally associated with stability in carbon-centered radicals. Thus, the presence of π-acceptor groups (such as CN or Ph) as π-substituents within R leads to enhanced stability, as does the capacity for hyperconjugative interactions provided by π-CH3 substituents. On the other hand, in the RAFT agents, the presence of π-CH3 groups or π-acceptor π-substituents in R results in destabilization. Here, methylation primarily induces unfavorable steric interactions. The π-acceptor groups destabilize the RAFT agents by reducing the capacity for delocalization of the sulfur lone pair onto the double bond (Reaction (15)).

\[
\begin{align*}
\text{S} & \quad \text{S} & \quad \text{S} \\
\text{S} & \quad \text{S} & \quad \text{S}
\end{align*}
\]

\[\Delta H_{\text{CT}}\]

\[
(15)
\]

The steric and electronic properties of R, therefore, influence chain transfer in two reinforcing ways—one effect on the RAFT agent and the opposite effect on the R• radical. These combined effects render the commonly-used R groups CH(CH3)Ph, C(CH3)2CN, and C(CH3)2Ph very good leaving-group radicals. However, it is not correct to
assume that a well-controlled polymerization will result if one simply chooses the best leaving group $R = (CH_3)_2Ph$. If $R*$ is too stable compared with the monomer, then the subsequent re-initiation step is disfavored, and polymerization will not proceed past the stage of the first polyRAFT agent. When faced with a new polymerization, a sensible initial approach would, therefore, be first to take into account the stability of the propagating radical (which is roughly measured by the stability of the monomeric radicals shown in Figure 5, and could be better measured using calculations on the dimers), and then choose an $R$ group for which $R*$ is only slightly more or less stable than $M*$.

The simplifications involved in deriving the structure-reactivity relationships just described are accompanied, of course, by a number of exceptional cases. One important case is where a system does not obey the usual correlation between kinetics and thermodynamics. For example, by using computational investigations, it has recently been found\[16]\ that in the xanthate-mediated polymerization of vinyl acetate, the rate constant for fragmentation of the RAFT-adduct radical $CH_3SC(\cdot)(Z)SCH_2OCOCH_3 (Z = OCH_3)$ is three orders of magnitude larger than that for the radical where $Z = O'Bu$. This result cannot be attributed to a steric effect of $Z$, however, because for the related RAFT-adduct radicals $CH_3SC(\cdot)(Z)$SCH$_2$OCOCH$_3$, the rate constants for $Z = OCH_3$ and $Z = O'Bu$ are nearly identical. The source of the discrepancy lies instead in an H-bonding interaction in the transition state for the fragmentation of $CH_3SC(\cdot)(OCH_3)SCH_2OCOCH_3$. A close contact takes place between the carbonyl oxygen and an OCH$_3$ hydrogen, which leads to significant stabilization, whereas no analogous interactions take place for the other three species.

A breakdown of the structure-reactivity trends can also occur if there are synergistic interactions between the groups $R$, $Z$, and $P_n$. For example, it has been shown\[18]\ that fragmentation of electron-withdrawing $R$-groups is enhanced by a homoanomeric effect in which the withdrawal of electron density from sulfur towards the $R$ group reduces the ability of sulfur to donate electron density to the radical center. If the $R$ group contains a $\pi$-acceptor substituent, this induces an altered CS–R conformation in which the unpaired electron is delocalized into a CS–R antibonding orbital. This not only weakens the S–R bond but is accompanied by a strengthening of the S–P$_n$ bond in compensation. As a result, altered chain-transfer efficiencies arise that would not have been predicted on the basis of $R*$ stabilities alone. Moreover, the homoanomeric interaction is further modulated by the nature of $Z$: for example, a fluorine substituent in the $Z$ position can inhibit the effect of a $\pi$-acceptor-containing $R$ group.\[22]\ This example, and the vinyl acetate example given above, emphasize the importance of conducting specific computational or experimental investigations once one has selected a range of candidate RAFT agents for a particular application.

### RAFT Agent Design

The ultimate goal of computational studies of RAFT polymerization is to design new and improved RAFT agents to tackle any specific control problem. One could envisage a two-stage approach in which one first utilizes the structure-reactivity relationships to select promising combinations of substituents, and then tests the candidate RAFT agents with direct calculations using model propagating radicals. Having established computationally that a certain RAFT agent is likely to be successful, one could then pursue experimental testing.

The kinetic requirements of a successful RAFT agent are now fairly well understood: it should have a reactive C=S bond ($k_{add}$ high) but the intermediate radical should undergo fragmentation at a reasonable rate (typically $K = k_{add}/k_{frag} < 10^6$ L mol$^{-1}$), the $R$ group should fragment preferentially from the intermediate radical in the pre-equilibrium but also be capable of reinitiating polymerization, and there should be no side reactions.\[15,97]\ Computational data shown in Table 2 and 3 and in Figure 4 and 5 can assist in choosing RAFT agents that satisfy these criteria. For example, if one predicted that a propagating radical was relatively stable, then, in order to provide good control, its addition to the C=S bond would need to be fast enough to compete with addition to monomer. One could then select a $Z$ group that destabilized the C=S bond to promote addition (i.e., $\Delta H_{frag}$ in Figure 4 is large). By contrast, if one predicted that the propagating radical was relatively unstable, then it would be necessary to ensure that the propagating radical did not become trapped for too long as the RAFT-adduct radical. In this case, one would choose a $Z$ group that destabilized the RAFT-adduct radical relative to the C=S compound (i.e., $\Delta H_{frag}$ is small). Amongst substituents displaying acceptable $\Delta H_{frag}$ values, one could further optimize control by choosing the $Z$ group that gave the lowest RAFT agent stability, and hence the fastest addition rates. Likewise, one could use $\Delta H_{CT}$ values (as in Figure 5) to choose the $R$ group, an optimal group usually having $\Delta H_{CT}$ value marginally lower than that of the model propagating radical. Having selected candidate RAFT agents on the basis of the simplified isodesmic measures, they could then be tested computationally through direct calculation of the addition-fragmentation kinetics in more realistic model systems.

There is a growing interest in using computational calculations as a basis for RAFT agent design. Matyjaszewski and Poli\[19]\ and Patten and Farmer\[20]\ have advocated the use of calculated chain transfer energies (Reaction (13)) as a basis for choosing appropriate $R$ groups for specified monomers. Matyjaszewski and co-workers\[19,23,24]\ and Tordo and co-workers\[25]\ have applied similar strategies to ATRP and NMP, respectively. Building on this work, the first computationally designed class of RAFT agents, the fluorodithioformates ($S=C(F)SR$ or ‘F-RAFT’) has
Recently, RAFT agents have been proposed that are capable of controlling monomers with stable propagating radicals and also those with unstable propagating radicals. These agents are different from other RAFT agents that can be used to control monomers with a benzyl leaving group. Instead, RAFT agents with an unstable leaving group (such as the xanthates) are considered to be more reactive and are capable of controlling monomers with a benzyl leaving group. However, the use of computational quantum chemistry is showing promise as a tool for studying complicated radical polymerization processes such as RAFT.

**Outlook**

With the use of computational quantum chemistry, it is now possible to obtain chemically accurate kinetic and thermodynamic parameters for the key steps of RAFT polymerization. This makes the technique an important complement to experimental investigation. Although several challenges remain, notably the treatment of solvent effects, one hopes that the trends towards increasing computer power and more efficient algorithms will render these problems tractable in the near future. Even now, computational techniques have already provided insights of value to kinetic modeling and structure-reactivity profiling in RAFT, and have led to the design of a new class of RAFT agents. In the future, a computational approach would be of benefit for investigating the more intricate problems of initialization and copolymerization. Considerable progress has also been made in applying computational chemistry to ATRP and NMP, and one can foresee further profitable studies in this direction.

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