Which side-reactions compromise nitroxide mediated polymerization?
Which side-reactions compromise nitroxide mediated polymerization?†

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The mechanism of the nitroxide mediated polymerization (NMP) is well understood, however less is known about the side-reactions that interfere and in certain cases severely compromise it. Experimental studies inevitably involve model fitting leading to at times contradictory conclusions as to which elementary side-reactions are behind the failure of a given NMP system. In the present work we use high-level quantum-chemical calculations to obtain the rate coefficients of the various side-reactions, both suggested previously and considered here for the first time, and first principles PREDICI kinetic simulations to identify the most deleterious side-reactions involved in the TEMPO, SG1 and DPAIO mediated polymerization of styrene, acrylate and methacrylate monomers. We show that the core mechanism for the thermal decomposition of alkoxyamines differs between the uni- and polymeric species, which often makes such experiments not suitable for modelling the NMP conditions. We also find that the main side-reaction responsible for the failure of TEMPO and SG1 in methacrylate homopolymerization is an intramolecular alkoxyamine decomposition (often referred to as ‘disproportionation’) via a Cope-type elimination, however in the case of SG1 the polymerization outcome is additionally affected by the equilibrium constant of alkoxyamine bond homolysis. On the basis of these findings, complemented by a thorough analysis of available experimental data, we define guidelines for minimising occurrence of the side-reactions and thus improving NMP. Finally, the accurate first principles rate parameters reported in this study should prove useful for subsequent kinetic modelling oriented at optimising different polymerization conditions.

Introduction

Nitroxide mediated polymerization (NMP)† is a reversible deactivation radical polymerization that employs the persistent radical effect‡ of a stable nitroxide (aminosilyl) radical (Scheme 1). It facilitates control of the structure and length of the polymer chains, whilst achieving high conversion and low polydispersity (PDI < 1.20). Since the seminal CSIRO research in the mid-eighties,§ successful NMP of various monomers and under a wide range of conditions has been achieved, and applied to the synthesis of a broad variety of well-defined functional polymers including block, graft and random copolymers, brushes, stars, dendrimers, hyperbranched polymers.‡,§,8

Unfortunately, the effectiveness of NMP is often affected and sometimes even dominated by the occurrence of side-reactions that interfere with the control and result in unreactive by-products.9 The most well-known of these – bimolecular self-termination of transient polymeric radicals P (reaction (7) in Scheme 1) – is minimised in a well optimised NMP because combination of these species with the persistent nitroxide radicals is kinetically preferential to their recombination with one another.27,9 Other side reactions include competitive N–OR homolysis in alkoxyamines,9 formation of mid-chain radicals10 and chain transfer to solvent,9 however these can be inhibited and even excluded relatively easily by selecting resistant initiating alkoxyamines and mediating nitroxide radicals, and optimising the experimental conditions.22 Today, the greatest concern is raised by another commonly considered, yet poorly understood side-reaction, described variously as a ‘disproportionation’, ‘H-transfer’ or ‘cross-termination’ (referring to its chemical outcome) or as a ‘chain-end degradation’ (referring to its site, see Scheme 1).9 Potentially, this detrimental process can disrupt control and livingsness of the polymerization and lead to increased polydispersity,11 and is assumed to be the main chain-stopping event in many NMPs.3,4,5 Moreover, dead chains P(–H) (i.e., macro-monomers), so formed, have terminal double bonds that are expected to propagate autooxidative damage and thus compromise the service life and performance of the resulting polymer.16

Furthermore, there is also the possibility of a back hydrogen transfer from the hydroxylamine product of this decomposition.
reaction to a propagating polymeric radical, resulting in a second dead polymer chain, PH (reaction (5) in Scheme 1).\textsuperscript{17,18} This reaction also reforms the nitroxide and thus completes the autocatalytic cycle of irreversible alkoxyamine decomposition, although at typical $P_{\text{init}}$ concentrations it is assumed to play only a minor role in NMP.

A number of different mechanisms have been proposed to account for the so-called H-transfer side-reaction between nitroxides and propagating polymeric radicals.\textsuperscript{8,9} It may occur either intermolecularly (radical pathway (1)–(2) with rate coefficient $k_{\text{H2}}$) or intramolecularly (non-radical pathway (3) with rate coefficient $k_{\text{H1}}$). For the latter process, two routes are possible depending on the attacking atom: (a) $\gamma$H-abstraction by the oxygen atom via a 4-membered cyclic transition state, yielding alkene and hydroxylamine directly and (b) $\gamma$H-abstraction by nitrogen atom via a 5-membered transition state, yielding N-oxide (a so-called Cope-type elimination)\textsuperscript{20a} that is assumed to quickly rearrange into a hydroxylamine via reaction (4). It is well recognized that experimental discrimination between these pathways is difficult or even impossible.\textsuperscript{8} Specifically, occurrence of the alkoxyamine decomposition via H-transfer is judged by the detection of the corresponding products, $\gamma$-OH and, more often, P(\text{-}H), yet the alkene chain ends are also formed in both self- and cross-termination (Scheme 2).\textsuperscript{14} A further complicating factor is that the quantitative experimental detection of hydroxylamine is strongly dependent on the oxygen content in the reaction atmosphere (Scheme 2).\textsuperscript{20a} Alternatively, the overall rate of the undesirable H-transfer is often measured by the decrease in the concentration of the alkoxyamine, in which case the possibility of it being consumed in some other, not yet identified side-reaction is neglected. As a result, in the words of Souaille and Fischer, “it seems impossible to predict the extent of inter- and intramolecular pathways to any degree of certainty, because the influencing factors are not clearly established”.\textsuperscript{15} Indeed, values for $k_{\text{H1}}$ and $k_{\text{H2}}$, reported in literature to date (Table 1), are not necessarily in agreement with each other and depend strongly on the measurement technique (e.g., whether it involves following the concentration profiles of the initial alkoxyamines and/or the forming unsaturated chain ends in thermolysis of unimolecular alkoxyamines or during NMP itself), as well as the assumptions and model-fitting often associated with it. For example, reported $k_{\text{H1}}$ are often derived simply from the time-dependence of NMR signals of alkoxyamine $\alpha$-protons ($H_{\alpha}$) and the forming double-bond protons ($H_{\text{db}}$), i.e.,
considered was the polymerization, however the only other side-reaction initiation, were found to be responsible for the loss of control in nitroxide radicals, relevant to their protective action (as hindered amine light stabilizers, HALSs) against thermo- and photo-oxidative degradation of organic materials.22 Our results for a model system involving TEMPO and a typical polyester fragment radical (such as 4 in Fig. 1) suggest that both intramolecular alkoxamine decomposition pathways (3a and b in Scheme 1) are energetically implausible, in contrast to intermolecular H-transfer (2) and the subsequent back H-transfer from TEMPOH (5). Additionally, abstraction of a β-hydrogen atom by a polymeric radical from the alkoxamine

\[ k_{HH} = -\ln \frac{H_s}{H_s + H_{db}} \]

in alkoxime thermolysis experiments under the assumption that alternative side-reactions are unimportant.25 Clearly, a stricter distinction is necessary for accurate kinetic modelling of NMP and design of strategies for minimising these side-reactions.

Undoubtedly, there is a lack of understanding of the unwanted side-reactions that disrupt nitroxide mediated polymerization, particularly of their mechanistic aspects, yet this information is crucial for their prevention.9 Recently, Bentein et al.31 performed an advanced kinetic modelling of TEMPO (2,2′,6,6′-tetramethylpiperidine-N-oxyl, A in Fig. 1) and SG1 (N-(2-methylpropyl)-N-[1-diethylphosphono-2,2-dimethylpropyl]-N-oxyl, B in Fig. 1) mediated polymerization of styrene using available experimental rate parameters. Hydrogen transfer reactions from the transient and persistent radicals to the styrene Diels–Alder adduct, formed during its thermal self-initiation, were found to be responsible for the loss of control in the polymerization, however the only other side-reaction considered was the P self-termination by recombination. Unfortunately, the rest of the potential side-reactions discussed above were omitted from the kinetic model, largely because accurate kinetic data was not available at the time.

This is a situation where computational modelling can provide meaningful insight into the underlying chemistry of these processes, which is inaccessible directly from experiments. Provided a high level of theory is used, accurate kinetic parameters for every potential side reaction can be obtained, independent of kinetic model-based assumptions. Using high-level ab initio calculations, we have recently investigated the diverse chemistry of nitroxide radicals, relevant to their protective action (as hindered amine light stabilizers, HALSs) against thermo- and photo-oxidative degradation of organic materials.22 Our results for a model system involving TEMPO

Table 1 Rate constants of H-transfer in different NMP systems, reported in literature

<table>
<thead>
<tr>
<th>Alkoxaminea</th>
<th>T, °C</th>
<th>Solventb</th>
<th>Exp.c</th>
<th>k_H</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEMPO-S A 1</td>
<td>120</td>
<td>DMSO</td>
<td>Therm.</td>
<td>3.0 × 10⁻³ s⁻¹</td>
<td>22</td>
</tr>
<tr>
<td>TEMPO-S A 1</td>
<td>125</td>
<td>Toluene</td>
<td>Therm.</td>
<td>4.8 × 10⁻⁶ s⁻¹</td>
<td>23</td>
</tr>
<tr>
<td>TEMPO-S A 1</td>
<td>140</td>
<td>Toluene</td>
<td>Therm.</td>
<td>4.5 × 10⁻³ s⁻¹</td>
<td>24</td>
</tr>
<tr>
<td>TEMPO-PS A 1</td>
<td>140</td>
<td>Toluene</td>
<td>Therm.</td>
<td>2.5 × 10⁻⁴ s⁻¹</td>
<td>24</td>
</tr>
<tr>
<td>TEMPO-PS A 1</td>
<td>125</td>
<td>Toluene</td>
<td>Therm.</td>
<td>4.7 × 10⁻⁶ s⁻¹</td>
<td>25</td>
</tr>
<tr>
<td>TEMPO-PBA A 2</td>
<td>120</td>
<td>BA</td>
<td>NMP</td>
<td>1.1 × 10⁻³ s⁻¹</td>
<td>26</td>
</tr>
<tr>
<td>TEMPO-PMMA A 3</td>
<td>130</td>
<td>MMA</td>
<td>NMP</td>
<td>1.4 × 10⁶ L mol⁻¹ s⁻¹</td>
<td>27</td>
</tr>
<tr>
<td>SG1–MMA B 3</td>
<td>75</td>
<td>Benzene</td>
<td>Therm.</td>
<td>1.7 × 10³ L mol⁻¹ s⁻¹</td>
<td>28</td>
</tr>
<tr>
<td>SG1–PMMA B 3</td>
<td>70</td>
<td>MMA</td>
<td>PREDICI</td>
<td>1.7 × 10³ L mol⁻¹ s⁻¹</td>
<td>29</td>
</tr>
<tr>
<td>C3 (R₅,₆ = Me)</td>
<td>100</td>
<td>Benzene</td>
<td>Therm.</td>
<td>1.5 × 10⁻⁵ s⁻¹</td>
<td>30</td>
</tr>
<tr>
<td>C3 (R₅,₆ = Me, R₃,₆ = Ph)</td>
<td>95</td>
<td>Benzene</td>
<td>Therm.</td>
<td>8.7 × 10⁻⁵ L mol⁻¹ s⁻¹</td>
<td>30</td>
</tr>
</tbody>
</table>

a Here and further ‘S’ stands for styrene, ‘BA’ – butyl acrylate, ‘MMA’ – methyl methacrylate, ‘P’ denotes corresponding polymeric fragment, see Fig. 1 for structures and acronyms. Letter-numeral notations in bold correspond to those in Fig. 1, subscript ‘n’ denotes polymeric fragment.

b ‘DMSO’ stands for dimethylsulfoxide. c Experimental methods: ‘Therm.’ refers to thermal decomposition of the corresponding alkoxamine, ‘NMP’ refers to polymerization in which alkoxamines in the first column are dormant species, ‘PREDICI’ refers to kinetic modelling using PREDICI software.

Fig. 1 Persistent nitroxide radicals and transient unimeric propagating radicals in NMP.
(reaction (6)), followed by its rapid decomposition into an aminyl radical and a ketone was found to play a key role in the catalytic cycle responsible for the high antioxidant efficiencies of HALS (see also Scheme S1 in the ESI). To the best of our knowledge, the role of this step in NMP of monomers containing an abstractable β-hydrogen (styrene, acrylates) has not yet been studied, while only low-level methods (such as UB3-LYP/6-311+G(3df,2p)//AM1 in the gas phase) have been used to investigate the H-transfer in NMP computationally.

In the present work we aim to assess the relative importance of these various proposed side-reactions in typical NMP systems with a view to suggesting strategies for their suppression. State-of-the-art quantum-chemical calculations are used to clarify the nature of these side-reactions and calculate their individual rate and equilibrium constants for a broad test set of common propagating radicals and NMP control agents from first principles. With the aid of available literature experimental data and without any fitting or parameterisation, we construct kinetic models of various NMPs and analyse them in order to explain the success or failure of these systems (and other associated experimental observations) and provide tools for predicting the performance of other nitroxides in controlling monomers of choice.

Theoretical procedures

In the present work, we have performed kinetic modelling for several model NMP systems under various scenarios (i.e., different initial concentrations and/or rate constants of different reaction steps) at 120 °C in the bulk solution of relevant monomers using PREDICI software. Accurate experimentally determined rate constants for the main equilibrium, propagation and chain-length-independent self-termination were taken from the literature; however, rate parameters of comparable consistency and reliability for the various side-reactions are not available. Therefore, we have employed quantum chemistry to determine them from first principles. Specifically, we used high-level composite ab initio G3(MP2)-RAD method in conjunction with B3LYP geometries and frequencies to obtain accurate gas-phase Gibbs free energies, and COSMO-RS (Conductor-like Screening MOdel for Realistic Solvents) method to model the solvent effects. This methodology has been previously shown to predict accurate values of the kinetics and thermodynamics of radical reactions, including the specific case of nitroxide mediated polymerization. All standard ab initio molecular orbital theory and density functional theory (DFT) calculations were carried out using Gaussian 09, Molpro 2009.1, ADF 2010.01 (ref. 45) and Q-Chem 3.2 and 4.0 (ref. 46) software packages. A detailed description of all the computational procedures and kinetic modelling, as well as full set of obtained results can be found in the ESL.

Results

In order to identify which side-reactions disrupt the controlled radical polymerization of styrene, methyl acrylate and methyl methacrylate (corresponding to propagating radicals P1, 2 and 3 in Fig. 1) mediated by the various commonly used nitroxides (TEMPO A, SG1 B and DPAIO (2,2-diphenyl-3-phenylimino-2,3-dihydroindole-N-oxyl) D in Fig. 1), we investigated the energetics of these processes. In doing so, we have considered the main equilibrium, propagation and self-termination, as well as other proposed side-reactions (collected in one scheme in Fig. 2). Our kinetic model utilised typical starting concentrations of the reactive species, available experimental rate constants for the main equilibrium, propagation and biradical termination of P, as well as rate coefficients for other side-reactions, obtained in this work from first principles (free of any model fitting) using high-level ab initio calculations, for five exemplary NMP systems under relevant conditions (Fig. 2). We find that the intramolecular pathway (3a) is kinetically improbable in all five studied systems, while reaction (3b) is highly endoergic in all systems except TEMPO–PMMA and SG1–PMMA, for which it was modelled as reversible. In contrast to unimolecular H-transfer (3), in-cage H-abstraction (2) has similar energetics in all investigated systems. Calculated rate coefficients for both types of H-transfer are, in general, noticeably different from the experimental values reported in the literature (Table 1), which reinforces the notion that the latter are more likely to correspond to the rate laws for individual measured observables (e.g., time-dependences of the alkoxamine or alkene chain ends concentrations) rather than the elementary steps in the kinetic scheme. On the other hand, our calculated k_re-t values are in a good agreement with those adopted by Bentein et al. Finally, β-H abstraction cannot occur in methacrylates as they lack the corresponding hydrogen atom and involves a comparatively high barrier in SG1–PBA system, but is viable in the TEMPO–PS polymerization.

Nonetheless, analysis of the individual rate coefficients and reaction total energies is insufficient to determine the most harmful side-reactions in such a complex multi-step process as NMP. Full kinetic modelling is thus necessary to account for the changing concentrations and to evaluate the quality of the polymerization (in terms of time needed to reach high monomer conversion, polydispersity of the resulting polymer and percentages of dead and defected polymer chains). Results of this modelling are now discussed in turn for the five studied polymerization systems.

Discussion

TEMPO-mediated polymerization of styrene

Historically, TEMPO (A) was the first nitroxide mediator that allowed successful radical polymerization of styrene. Nowadays, TEMPO (or its derivatives) is still the control agent of choice for homopolymerization of styrene and its copolymerization with some acrylate and methacrylate monomers, primarily due to a high equilibrium constant of combination/decomposition between persistent and transient radicals and appreciable thermal self-initiation of styrene (Fig. 2). One of the common approaches to studying the H-transfer side-reactions in NMP involves thermolysis experiments of the unimeric alkoxamines. However, the observed extent of irreversible alkoxylamine decomposition in such model studies is too large to be consistent with the successful TEMPO-mediated polymerization of styrenes, because unimeric alkoxamines

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lack the penultimate unit effect,48 present in the macroinitiators and dormant macroalkoxyamines. This is reflected in the fractions of disproportionation, fD, and amounts of alkene produced in the thermolysis of unimeric alkoxyamines, overestimated compared with the dimeric and polymeric analogues.23,24,50 However, the possibility of the chemistry behind the decomposition of unimeric vs. polymeric alkoxyamines being principally different is not widely appreciated. Yet, experimental evidence reveal that in unimeric alkoxyamines, e.g. A1, H-transfer occurs primarily intermolecularly,24,51,52 whilst thermal decomposition of macroalkoxyamine A1n is slower and is not affected by addition of free TEMPO.25,53 These observations can be explained on the basis of our calculated rate constants of H-transfer reactions (Scheme 3). In both systems (uni- and dimeric) an intramolecular pathway is disfavoured kinetically, while intermolecular H-abstraction has comparable energetics. At the same time, the β-H abstraction, which has first-order kinetics with respect to alkoxyamine concentration, but not to free nitroxide, is dramatically faster in dimeric species. It therefore appears that unimeric and polymeric alkoxyamines are deactivated in fundamentally different elementary reactions that follow divergent kinetics.

But even if appropriate (oligo- or polymeric) alkoxyamines are studied, their thermolysis in inert solvents does not necessarily provide a realistic insight into the side-reactions disrupting styrene NMP. This is because styrene monomers are capable of thermal self-initiation, which is competitive with the H-transfer to an extent that the latter process is effectively suppressed at sufficiently high styrene concentrations.17,53,55 Results of our kinetic simulations of TEMPO-mediated polymerization of styrene (Fig. 3, see Fig. S1 and 2 of the ESI for details†) are consistent with the various experimental and theoretical studies:15,18,31,47,52,56,57 high monomer conversions (>90%) and low polydispersities (ca. 1.2) are achieved with by-products forming in only minor quantities. The main side-product, PP, is formed via biradical combination of the transient radicals (reaction (7) in Fig. 2).

Unfortunately, significant irreversible decomposition of alkoxyamines is the reason behind the unsatisfactory
performance of TEMPO and its analogues in controlling polymerization of monomers other than styrenics.\textsuperscript{a} Considerable H-transfer, observed in TEMPO-mediated polymerization of butyl acrylate,\textsuperscript{26} is presumed to occur largely \textit{via} a non-radical alkoxylamine decomposition pathway (3b) (Fig. 2).\textsuperscript{52} Attempts have been made to enhance the performance of cyclic nitroxides in the NMP of acrylates by introducing bulky substituents into the \( \alpha \)-position of the nitroxide moiety, and reasonable success has been achieved using alkoxylamine initiator K2 with \( R = \text{Et} \) or \( \text{nPr} \), though with \( R = \text{Me} \) control and livingness were lost.\textsuperscript{38} It therefore appears that a sterically hindered nitroxide moiety is a desired feature as, on one hand, it brings \( K_{eq} \) down to a range of values required for controlled and living radical polymerization (by lowering \( k_a \) and increasing \( k_d \) compared to TEMPO) and, on the other hand, diminishes the ability of such nitroxides to abstract hydrogen atoms from polymeric radicals.

**SG1-mediated polymerization of acrylates**

Efficient controlled and living homopolymerization of a wider range of monomers (acrylates, acrylamides, 1,3-dienes, etc.) became possible with the development of acyclic nitroxides (e.g., 2,2,5-tri-methyl-4-phenyl-3-azahexane-3-nitroxide TIPNO, \( \text{B} \) in Fig. 1) by Hawker et al.\textsuperscript{29} and their phosphorylated analogues, such as SG1 (also referred to as DEPN, \( \text{B} \) in Fig. 1) by Tordo and coworkers.\textsuperscript{15b} These nitroxides are bulkier, which facilitates direct NO–C homolysis that can thus occur at lower temperatures with improved polymerization outcomes.\textsuperscript{3,59,60,61} Indeed, our kinetic simulations reveal that SG1-mediated polymerization of PBA is expected to succeed and is not disrupted by various side-reactions (Fig. 4, see Fig. S3 of the ESI for details).\textsuperscript{7} In agreement with the available experimental data, our modelled NMP of this system at 120 °C proceeds noticeably faster than that of TEMPO–PS, although the resulting PDI values produced in our simulations are lower than typically observed.\textsuperscript{15a,k} Lastly, both our calculations (Fig. 2) and experiments\textsuperscript{84} indicate that SG1 nitroxide is more resistant against H-abstraction compared with TEMPO due, primarily, to its increased steric hindrance, as discussed above.

In addition to the acyclic nitroxides, changing the ring size in the cyclic species (from 6-membered TEMPO) offers an alternative approach to improving NMP. For example, 5-membered ring nitroxides, such as TEMIO (2,2′,5,5′-tetramethyl-4-oxoimidazolidine-N-oxyl) \( \text{F} \), PROXYL (2,2′,5,5′-tetramethylpyrrolidine-N-oxyl) \( \text{G} \) and TMIO (1,1′,3,3′-tetramethylsindoline-N-oxyl) \( \text{H} \) in Fig. 1 form more thermally stable alkoxylamines and afford lower polydispersity indices and higher conversions for styrene and acrylate NMP compared with TEMPO, suggesting the former are less prone to the H-transfer.\textsuperscript{13,25,30,42} Nitroxides with a larger ring size, \textit{e.g.} I and J, afford reasonably efficient NMP of styrene and acrylates due to higher \( k_d \), although their decomposition \textit{via} H-abstraction is also faster compared with 6-membered species.\textsuperscript{63}

**NMP of methacrylates**

Until recently, the successful polymerization of methacrylates and other 1,1′-disubstituted monomers represented possibly the greatest challenge for the NMP. As noted above, there are no reports of success in controlling MMA polymerization with TEMPO (without using additives or unconventional approaches). It is well known that methacrylates are more prone to the H-transfer side-reaction\textsuperscript{32} because, firstly, unlike styrenics, these monomers are incapable of thermal self-initiation and, secondly, they are bulky which causes shielding of a radical centre in the corresponding propagating radicals and, ultimately, very high \( k_a \) (Fig. 2). However, while some studies conclude that the H-transfer in TEMPO–PMMA system, investigated predominantly \textit{via} thermolysis experiments on unimolecular alkoxylamines (such as A3), follows the bimolecular (radical) pathway (2),\textsuperscript{52} others highlight the contribution from an intramolecular Cope-type decomposition (3b).\textsuperscript{52} Our results (see Fig. S4 of the ESI\textsuperscript{1}) confirm the predominant role of the latter process in spoiling this NMP. If this reaction were absent, conversion of almost 90% would be achievable and by-products (such as dead polymer chains, P–P and P–(−H), and hydroxylamine NOH) would be formed in insignificant amounts of \( <10^{-4} \text{ mol L}^{-1} \) (Fig. 5). At the same time, turning all H-transfer reactions involving nitroxide and/or alkoxylamine off affords an even better performance and, in particular, polymerization rate enhancement (Fig. 5, see also Fig. S4 of the ESI\textsuperscript{1}), which suggests that intermolecular H-transfer (2) and back H-transfer (5) also contribute to the failure of TEMPO-mediated NMP of methacrylates.
Likewise, it is not surprising to witness the failure of SG1 in methacrylate homopolymerization. Both species are sterically hindered, which leads to an equilibrium constant four orders of magnitude lower than needed for an efficient NMP (Fig. 2). Nevertheless, successful polymerization of MMA with B3 (BlocBuilder®), R = H in Fig. 1) and K1 initiators was achieved by adding a small amount of styrene, and in which case the propagating unit in P is always a styryl and the constant of its equilibrium with the nitroxide is sufficiently high (Fig. 2, see reaction sequence (A) in Scheme S2 of the ESI†). Interestingly, the reverse polymerization procedure (i.e., styrene radicals instead of monomers) is deemed to fail because of the dominating H-transfer side-reaction (reaction sequence (B) in Scheme S2 of the ESI†).

Thus, it is clear that SG1-mediated polymerization of methacrylates is compromised by an insufficiently high equilibrium constant, yet experimental evidence on the H-abstraction reaction in this system is somewhat contradictory. Specifically, while no appreciable amounts of H-transfer products were detected in some studies, other experiments identify intermolecular pathway (2) as the main chain-stopping event.

Our kinetic simulations (see Fig. S5 of the ESI†) suggest that, similarly to the TEMPO–PMMA system, the most damaging H-transfer reaction is intramolecular pathway leading to N-oxide (3b), although other side-reactions also contribute to the failure of this NMP. Consistent with experimental observations, we find that excess of free nitroxide control agent is detrimental at the early stages of polymerization (see Fig. S6 of the ESI†). However, in contrast to TEMPO–PMMA (Fig. 5), even when all H-transfer side-reactions are eliminated, polymerization in SG1–PMMA system still fails due to rapid decomposition of alkoxynitroxides and biradical coupling of released P (see Fig. S5 of the ESI†). Success can be achieved when not only the intramolecular Cope-type elimination (3b) is turned off, but when $k_d$ and $k_c$ are additionally adjusted to afford larger $K_{eq}$ too (Fig. 6).

**DPAIO-mediated polymerization of methacrylates**

Successful conventional homopolymerization of methacrylates was finally achieved with the introduction of an indole-based nitroxide DPAIO (D in Fig. 1). Presumably, the H-transfer side-reaction is negligible in this system due to a lower reactivity of DPAIO compared to TEMPO (Fig. 2). The radical in D is delocalised by the conjugated aromatic system and $C=\text{NPh}$ group, unlike TEMPO or SG1, in which unpaired electron is localised largely on the NO moiety (see Fig. S7 of the ESI†). This is why DPAIO and other aryl nitroxides succeed in controlling MMA, although the equilibrium constants of macroalkoxynitroxides composed of DPAIO and transient radicals other than those derived from 1,1′-disubstituted monomers are expected to be unsuitable (too high $k_c$ and too low $k_d$) for NMP. Moreover, stabilisation of the unpaired electron in DPAIO promotes competitive direct N–OC homolysis of alkoxynitroxides (see Fig. S8 of the ESI†). While NO–C homolysis is still predominant when the leaving radical P is resonance stabilised, as is the case of methacrylate, DPAIO-mediated polymerization of monomers lacking such stabilisation in the corresponding P is deemed to fail.

The extent and mere occurrence of the H-transfer reaction between DPAIO and methacrylate radicals is not entirely clear from the experimental results in the literature. Interestingly, most of the side-reactions in this system are overruled in the present work: the transition state of the intramolecular alkoxynitroxide decomposition (3a) was not located, pathway (3b) was found improbable on thermodynamic grounds (Fig. 2) and pathway (6) is not possible in this system due to the absence of an...
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values for rate coeﬃcients for most of these reactions are reported in this work for the first time. Upon analysing the calculated reaction energetics and results of the kinetic modeling, we reach the following conclusions.

(1) Experiments on thermal decomposition of unimeric alkoxyamines in inert solvents are not necessarily appropriate for modeling the deactivation of dormant species in NMP. Experimentally, products of such thermolysis studies and conclusions on the decomposition mechanisms derived from them are often quite different from those in the actual polymerization. Results of our kinetic modeling reveal that decomposition of alkoxyamines in these two different types of experiments can occur via principally different mechanisms;

(2) In all five studied systems, intermolecular H-transfer between the nitroxide and propagating radicals was found to have very similar energetics (Fig. 2). Kinetic simulations show that this process does not affect control and outcomes of the polymerization to any significant extent;

(3) In all five studied systems intramolecular decomposition of alkoxyamine leading directly to alkene and hydroxylamine was found to be mildly exoergic but highly disfavoured kinetically (Fig. 2). In the three successful NMP systems the alternative intramolecular pathway – Cope-type elimination of N-oxide followed by its transformation into hydroxylamine – is highly improbable on thermodynamic grounds (Fig. 2). However, in the two unsuccessful systems this pathway is thermoneutral with mild activation barriers. As a result, this reaction appears to be the main source of irreversible alkoxyamine decomposition leading to unsaturated chain ends in both TEMPO- and SG1-mediated polymerizations of MMA;

(4) TEMPO-mediated NMP of PMMA is disrupted solely by H-transfer reactions, while in the case of SG1 even if these reactions were eliminated, polymerization would still fail due to inherent instability of the alkoxyamine species (low $K_{eq}$);

(5) In the case of monomers forming alkoxyamines with an abstractable β-hydrogen R$_1$R$_2$NO with $K_{eq}$ values of the corresponding alkoxyamines are still sufficiently high;

(6) Literature evidence suggests that side-reactions in NMP of many monomers may be potentially minimised by using nitroxides of a smaller ring size (5-membered instead of 6-membered) and with steric bulk around NO moiety (such as α-ethyl and cyclohexyl substituents), provided $K_{eq}$ values of the corresponding alkoxyamines are still sufficiently high;

(7) Optimisation of NMP should involve not only matching the properties of the controlling nitroxide to a chosen monomer, but also the resistance of initiator alkoxyamines towards the various side-reactions discussed here.

Conclusions

In the present work, we have identified which side-reactions interfere with nitroxide mediated polymerization for five examples: three successful polymerization systems (TEMPO–PS, SG1–PBA and DPAIO–PMMA) and two failing systems (TEMPO–PMMA and SG1–PMMA). We combined available literature experimental values for rate coeﬃcients of the key NMP steps with those for the side-reactions calculated in this study from ﬁrst principles using high-level computational methodology under experimentally relevant conditions, and performed ﬁrst-principles kinetic modelling of these NMPs using PREDICI software without recourse to parameter ﬁtting of any kind. In addition to the side-reactions suggested in the literature – inter- and intramolecular alkoxyamine H-transfers – we also included in our kinetic model reactions that, to the best of our knowledge, have not been previously considered in detail – alkoxyamine decomposition via β-hydrogen abstraction, conversion of N-oxide into hydroxylamine, and back hydrogen transfer from hydroxylamine to the propagating radical. Rate coeﬃcients for most of these reactions

are reported in this work for the first time. Upon analysing the calculated reaction energetics and results of the kinetic modeling, we reach the following conclusions.

(1) Experiments on thermal decomposition of unimeric alkoxyamines in inert solvents are not necessarily appropriate for modelling the deactivation of dormant species in NMP. Experimentally, products of such thermolysis studies and conclusions on the decomposition mechanisms derived from them are often quite different from those in the actual polymerization. Results of our kinetic modeling reveal that decomposition of alkoxyamines in these two different types of experiments can occur via principally different mechanisms;

(2) In all five studied systems, intermolecular H-transfer between the nitroxide and propagating radicals was found to have very similar energetics (Fig. 2). Kinetic simulations show that this process does not affect control and outcomes of the polymerization to any significant extent;

(3) In all five studied systems intramolecular decomposition of alkoxyamine leading directly to alkene and hydroxylamine was found to be mildly exoergic but highly disfavoured kinetically (Fig. 2). In the three successful NMP systems the alternative intramolecular pathway – Cope-type elimination of N-oxide followed by its transformation into hydroxylamine – is highly improbable on thermodynamic grounds (Fig. 2). However, in the two unsuccessful systems this pathway is thermoneutral with mild activation barriers. As a result, this reaction appears to be the main source of irreversible alkoxyamine decomposition leading to unsaturated chain ends in both TEMPO- and SG1-mediated polymerizations of MMA;

(4) TEMPO-mediated NMP of PMMA is disrupted solely by H-transfer reactions, while in the case of SG1 even if these reactions were eliminated, polymerization would still fail due to inherent instability of the alkoxyamine species (low $K_{eq}$);

(5) In the case of monomers forming alkoxyamines with an abstractable β-hydrogen R$_1$R$_2$NO–CHR$_3$R$_4$ (such as styrene), this β-hydrogen abstraction has the greatest influence on the thermolysis of the corresponding alkoxyamines and can potentially disrupt the polymerization as well. Interestingly, while this reaction is undesired in NMP, it is a key step in the antioxidative protection afforded by the nitroxides;

(6) Literature evidence suggests that side-reactions in NMP of many monomers may be potentially minimised by using nitroxides of a smaller ring size (5-membered instead of 6-membered) and with steric bulk around NO moiety (such as α-ethyl and cyclohexyl substituents), provided $K_{eq}$ values of the corresponding alkoxyamines are still sufficiently high;

(7) Optimisation of NMP should involve not only matching the properties of the controlling nitroxide to a chosen monomer, but also the resistance of initiator alkoxyamines towards the various side-reactions discussed here.

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Notes and references

36. Zero rate constants are given for the following cases: (i) reaction is highly endoergic and is unlikely to be significant, therefore its barrier was not calculated; (ii) species participating in this reaction are not expected to form in appreciable amount, therefore its barrier was not calculated; (iii) dormant alkoxamine species do not have an abstractable β-hydrogen; (iv) transition state structure was not located. See ESI for details.†
37. The chain-length dependence of the termination rate coefficient was not included in the present study in order to allow direct comparison with other side-reactions for modelled dimeric species. For a review of chain-length effect on $k_\alpha$, see C. Barner-Kowollik and G. T. Russell, *Prog. Polym. Sci.*, 2009, 34, 1211.


49 Fraction of disproportionation is defined as $f_D = k_{413}/k_4$ for a non-radical intramolecular pathway and as $f_I = k_{413}/(k_{413} + k_4)$ for a radical intermolecular pathway.


54 Not capable to polymerize, for example toluene.


57 Experimentally measured bond dissociation enthalpies (gas phase, 25 °C) of O–H bond in TEMPO–H is in the range of 291.2–297.7 kJ mol$^{-1}$, calculated values under the same conditions are 294.4 kJ mol$^{-1}$ for TEMPO–H bond and 402.3 kJ mol$^{-1}$ for N–H bond in TEMPH.$^{32}$


