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Structural Influences in Nitroxide Mediated Controlled Radical Polymerisation

Alistair James Reid

A thesis submitted to the Department of Chemistry, University of Durham in fulfilment of the requirements for the degree of Doctor of Philosophy

2004

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The encouragement and support of my friends and family have been much appreciated throughout my studies. In particular I'd like to thank Lauren and Andrew for enduring the extremes of enthusiasm and despair which accompany any PhD programme.

Abstract

This work describes the synthesis and application in controlled radical polymerisation of several novel pyrrolidine-N-oxyl, PROXYL, based nitroxide and alkoxyamines species bearing a variety of substituents adjacent to the nitroxide functionality.

Through variation of the nitroxide electronic structure a variation in rate of styrene polymerisation was observed and one nitroxide demonstrated the ability to mediate polymerisation of *n*-butyl acrylate. In an attempt to rationalise this behaviour examination was carried out on model species studying the influence of nitroxide structure on thermal dissociation of alkoxyamine carbon to oxygen bond and the propensity of alkoxyamines towards hydrogen transfer disproportionation. It is suggested that the reduced propensity for this hydrogen transfer disproportionation in addition to the rate of the alkoxyamine homolysis is a key factor in determining the activity of nitroxide in mediated controlled radical polymerisation.

The results of this study are placed within the context of the current state of knowledge in nitroxide mediated controlled radical polymerisation.

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Chapter 1 - Introduction

Macromolecular Chemistry[1]

The manufacture, processing and end use properties of polymers are of huge commercial importance to both producers and customers and there can be few aspects of modern living which do not involve synthetic polymers in some shape or form. Significant progress in the understanding of macromolecular chemistry has been made over the eighty years which have passed since the first recognition of the polymeric nature of widely used natural and synthetic materials and the first steps in deliberate synthesis of polymers. Although synthetic techniques have been developed which allow preparation of a wide variety of macromolecular structures, there continues to be significant academic and industrial interest in potential improvement over current polymerisation methodologies.

The majority of polymers manufactured industrially are produced by an addition polymerisation process in which a long chain, or macromolecular, species is generated by a single chain reaction. This process utilises a propagating reactive intermediate referred to as an active centre. The active centres commonly used in polymerisation are radical, ionic or dipolar species. The active centre reacts with a monomer molecule adding it to the growing polymer chain with regeneration of the active centre [Figure 1].

[1] Cowie, J.M.G., Polymers: Chemistry and Physics of Modern Materials, **1991**, 2nd Edition, Blackie Academic and Professional

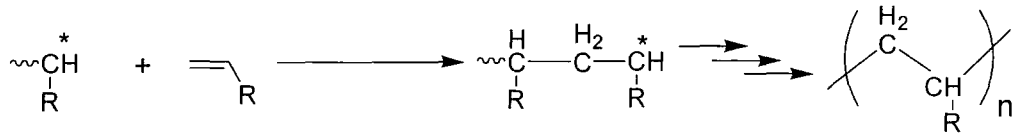


Figure 1 Addition polymerisation of vinyl monomer through an active centre

The choice of which active centre is used is dictated by the desired product and the monomers with which we wish to work. The advantages and disadvantages associated with different polymerisation methodologies require that a balance is struck between the application value and production costs. Bulk, low value, polymerisations require a cheap raw material and synthetic route while very high value applications allow the use of more expensive raw materials and complex synthetic routes.

There is significant interest from researchers both in academia and industry in exploring and developing the middle ground between these two areas, allowing more economically and synthetically accessible routes to tailored macromolecular species.

Free Radical Polymerisation

Much of the synthetic polymer currently produced is manufactured by a free radical process from monomer containing a vinyl unsaturation. The active propagating intermediate in free radical polymerisation is a radical located at the growing polymer chain end. These propagating radicals are generated using an initiating species. Initiators are used which generate free radical species in a number of ways; by ultraviolet irradiation [Figure 2], thermally [Figure 3] or by a redox process [Figure 4].

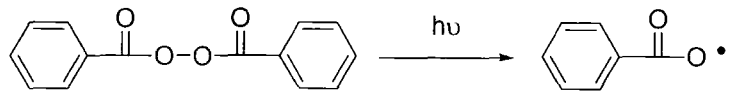


Figure 2 Ultraviolet initiation of benzoyl peroxide

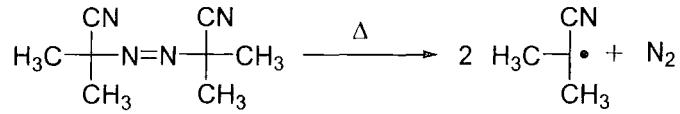


Figure 3 Thermal initiation of azoisobutyronitrile

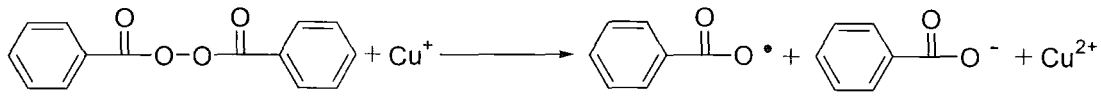


Figure 4 Redox initiation of benzoyl peroxide

A wide variety of initiators are commonly available, their selection being determined by the chosen polymerisation conditions. The formation of primary radicals by an initiator is by no means a straightforward reaction and has been the subject of significant study in its own right.

The reaction of the primary radical formed from initiation [Figure 5] with monomer containing an unsaturated vinyl group results in the formation of a new bond between the initiating species and the monomer and regeneration of a propagating radical [Figure 6]. This propagating radical will continue to add monomer with regeneration of the radical throughout its lifetime [Figure 7].

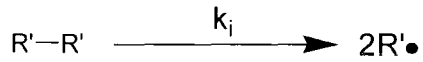


Figure 5 Initiation

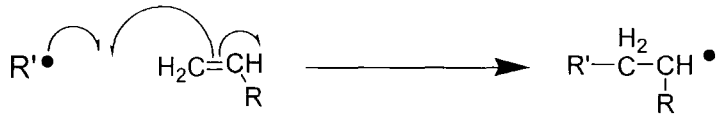


Figure 6 Addition of primary radical to monomer

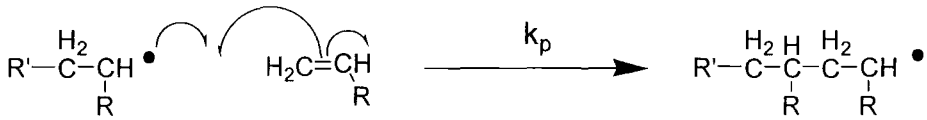


Figure 7 Propagation

The free radical polymerisation of vinyl monomers is synthetically very robust, compatible with a large variety of monomer functionalities with no special requirements for monomer and solvent purity. Free radical polymerisations may be carried out in the presence of water with the only precautions required being the removal of any radical inhibitors present in the monomer and the exclusion of oxygen. Care is often taken over the removal of oxygen from the polymerisation as the reaction of oxygen with the propagating carbon centred chain end radicals results in a reduction in polymerisation rate and introduces peroxide functionality into the backbone causing chain scission and broadening of the product molecular weight distribution.

The reaction of a propagating radical species with vinyl monomer operates under kinetic rather than thermodynamic control. Consequently, there is limited selectivity between differing vinyl species and often copolymerisation of dissimilar monomers is possible.

New material properties are often accessible without the synthesis of novel monomeric species through preparation of copolymers in which two or more monomer species are incorporated into the polymer backbone. The inclusion of different monomer species along a common backbone removes many of the problems caused by poor mixing associated with attempts to achieve novel material properties through blending dissimilar polymers.

Dissimilar monomers may be considered as being incorporated into a single chain in a three distinct ways: a statistical copolymer in which monomer is added to the growing backbone in a non selective random fashion; an alternating copolymer in which monomers are added in regularly in alternating fashion; and a block copolymer in which monomers are incorporated as discrete blocks although the

reality often lies somewhere between these clear cut extremes. The incorporation of monomer into polymer chain, on a simplistic level, is determined by the rates of the four potential addition reactions [Figure 8], each of the two possible chain end radical species can either react with the corresponding monomer (self propagation) or dissimilar monomer (cross propagation).

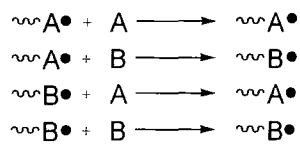


Figure 8 Potential propagation steps in radical copolymerisation

Under steady state conditions equations can be written describing the rate of incorporation for each monomer, [Equation 1] and [Equation 2].

$$-\frac{d[A]}{dt} = k_{AA}[A][A\cdot] + k_{BA}[A][B\cdot]$$

Equation 1

$$-\frac{d[B]}{dt} = k_{BB}[B][B\cdot] + k_{AB}[B][A\cdot]$$

Equation 2

Where k_{xy} represents the rate constant for the reaction of propagating radical x with monomer y.

Combination of these equations results in the instantaneous copolymer equation, [Equation 3].

$$\frac{d[A]}{d[B]} = ([A]/[B])\left(\frac{r_A[A]+[B]}{[A]+r_B[B]}\right)$$

Equation 3

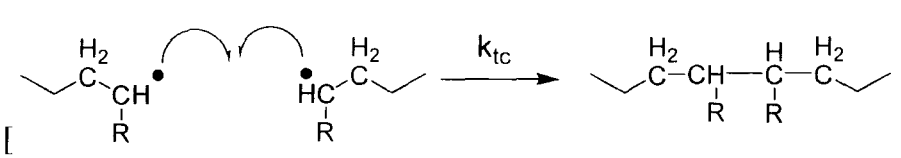
Where $k_{AA}/k_{AB} = r_A$ and $k_{BB}/k_{BA} = r_B$. These reactivity ratios, r_A and r_B describe the selectivity of the reaction between a propagating chain end and similar or dissimilar

monomer. The copolymer equation allows calculation of monomer incorporation into the polymer backbone.

If the reactivity ratios have been determined for a given combination of monomers under the polymerisation conditions it should be possible to calculate the level of incorporation of monomer into the chain at any point during the polymerisation. In a batch polymerisation where one monomer is preferentially incorporated the concentration of each component will change over time, altering the subsequent incorporation of monomer into the chain. This phenomena is termed composition drift. As a result of composition drift the copolymer equation is referred to as the instantaneous copolymer rate equation.

In polymerisations in which $r_A \approx r_B \approx 1$ there is little or no preference of either chain end for either monomer resulting in formation of a random copolymer. Where $r_A = r_B = 0$ each polymer radical chain end preferentially reacts with the dissimilar monomer and this results in an alternating structure. If $r_A > 1$ and $r_B < 1$ monomer A will be incorporated preferentially into the backbone resulting in a compositional drift along the chain as monomer A is depleted changing the incorporation ratios. For r_A and r_B both greater than one each chain end species will preferentially react with the corresponding monomer resulting in a blocky structure.

The use of a free radical active centre does not result in a "living" polymerisation. The propagating radical is a transient species and may by removed by one of several termination processes leading to the formation of a "dead" polymer chain unable to undergo further propagation. Bimolecular termination of a growing radical chain end may occur by either the coupling of two radicals in combination termination



[

Figure **9**] or by the extraction of a β hydrogen by one chain end from another in disproportionation termination [Figure 10]. Chains may also be terminated by a transfer reaction to another component of the polymerisation medium such as monomer [Figure 11].

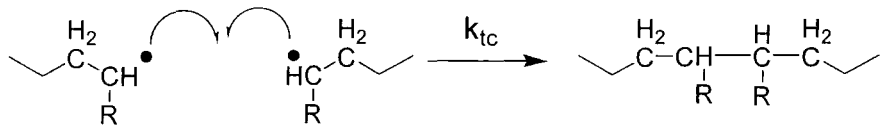


Figure 9 Chain termination by combination

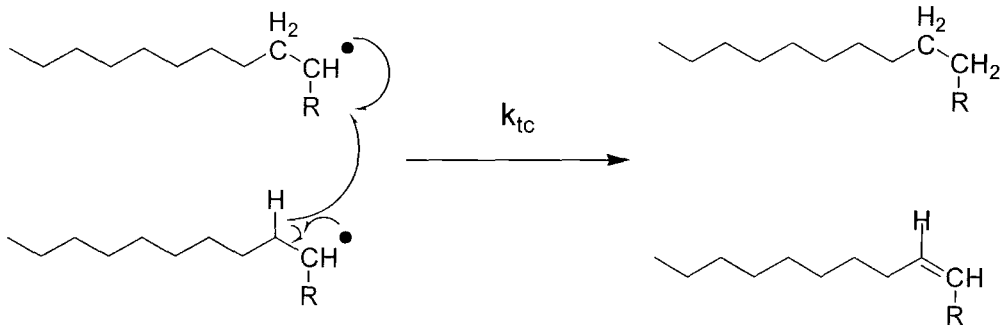


Figure 10 Chain termination by disproportionation

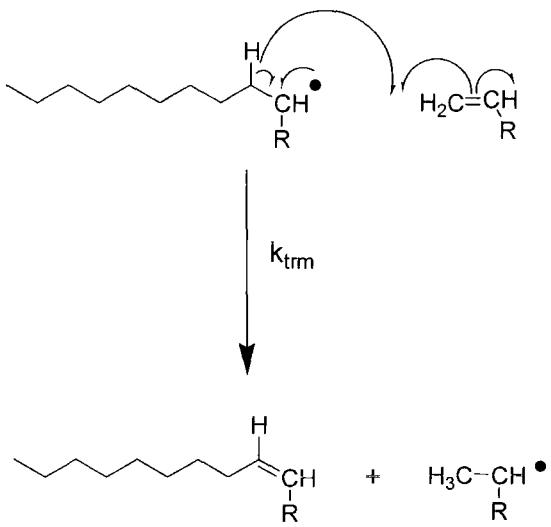


Figure 11 Chain termination by transfer to monomer

Molecular Weight Distribution in Radical Polymerisation

The effect of termination in free radical addition polymerisations is to introduce a random finite lifetime of the growing polymer chain. As each growing chain has a

chance of being terminated at any point throughout its life, the polymer product obtained is a statistical mixture of polymer chains of differing molecular weights. A high molecular weight product is obtained early in the polymerisation lifetime and the polymer molecular weight distribution which remains essentially the same throughout the polymerisation.

The material and chemical properties of a polymeric species are intimately related to the chain length and therefore the product molecular weight is of some importance. In a typical molecular weight distribution shown by mole fraction [Figure 12] we see a statistical distribution of polymer fractions from low to high molecular weight material with a peak corresponding to the most frequently occurring chain length.

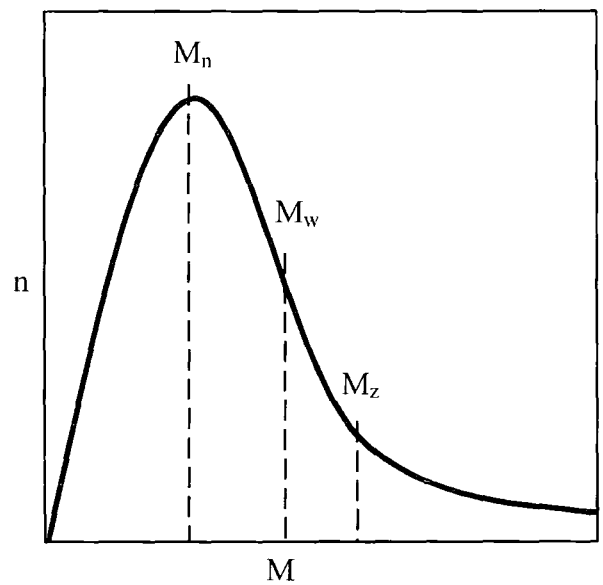


Figure 12 Typical molecular weight curve

The molecular weight of a polymer which exists as a mixture of fractions each with different individual molecular weights can be defined in a number of complimentary ways. Number average molecular weight, M_n [Equation 4].

$$M_n = \frac{\sum N_i M_i}{\sum N_i} = \frac{\sum w_i}{\sum (w_i / M_i)}$$

Equation 4

Where N_i and M_i are the number and mass of molecules of each species i and w_i is the mass of a component present.

Weight average molecular weight, M_w, is similarly defined, [Equation 5].

$$M_w = \frac{\sum N_i M_i^2}{\sum N_i M_i} = \frac{\sum w_i M_i}{\sum w_i}$$

Equation 5

Viscosity average molecular weight, M_z, defined by [Equation 6].

$$M_z = \frac{\sum N_i M_i^3}{\sum N_i M_i^2} = \frac{\sum w_i M_i^2}{\sum w_i M_i}$$

Equation 6

These measures of molecular weight allow definition of some numerical description of the molecular weight curve. The breadth of the molecular weight curve or molecular weight distribution is commonly described by the polydispersity, or heterogeneity, index, [Equation 7].

$$PD = \frac{M_n}{M_w}$$

Equation 7

A polydispersity of one indicates that the polymer is monodisperse and consists entirely of or uniform chains. The higher the polydispersity index the broader the molecular weight distribution.

Gel, or Trommsdorf-Norrish Effect

The industrial application of free radical polymerisation is complicated by the gel, or Trommsdorf-Norrish, effect. This occurs in polymerising systems in which, as the viscosity increases the individual reactions of the free radical polymerisation become diffusion limited at different viscosities. Bimolecular termination becomes diffusion limited first as a consequence of reduction in the rate of diffusion of polymeric species reducing the incidence of radical/radical collision. With the rate of loss of radicals greatly reduced the propagating radical concentration subsequently increases resulting in an increased rate of polymerisation, or autoacceleration, and resultant large exotherm. This auto-accelerated polymerisation occurs until a glassy solid is formed and monomer diffusion becomes reduced causing a reduction in the rate of propagation reaction [Figure 13].

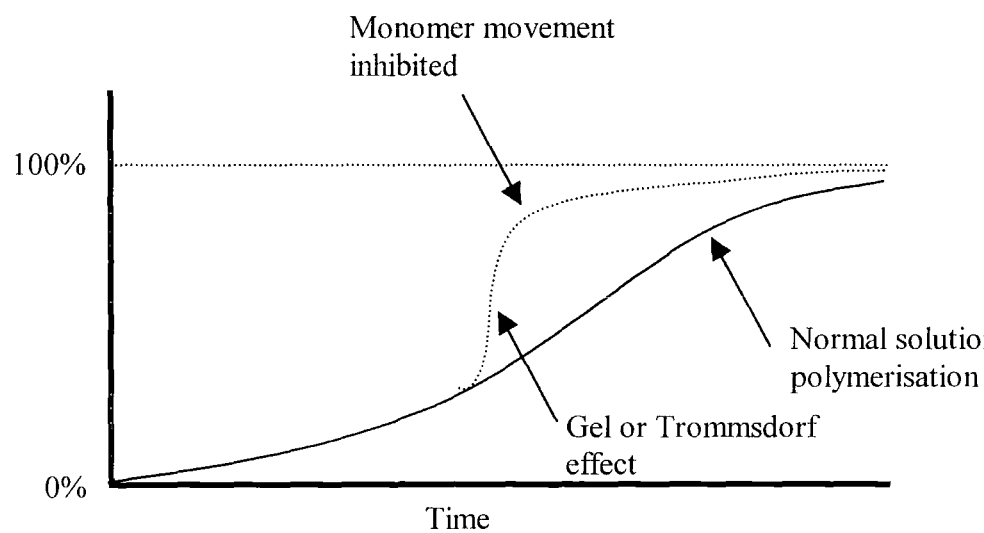


Figure 13 Gel, or Trommsdorf-Norrish, effect

In large vessels where heat transfer is poor the consequences of autoacceleration can become serious. As a consequence of the gel effect radical polymerisations in industry are generally carried out in dispersed media either solution, suspension or emulsion.

Ionic Polymerisation

As alternatives to free radical active centres addition polymerisations may be carried out using a charged anionic or cationic end group with an associated counterion as the active end group. Cationic polymerisations may be initiated by Lewis acids or Freidel-Crafts catalysts, protonic acids or acid surfaces, or carbenium acid salts. Propagation occurs through head to tail addition of vinyl monomer to the carbenium ion with regeneration of the carbenium ion [Figure 14].

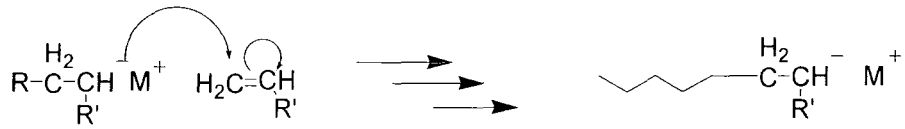


Figure 14 Cationic addition polymerisation

Termination in cationic addition polymerisation can occur by rearrangement of the ion pair, (unimolecular termination) [Figure 15] or through bimolecular transfer reaction with monomer (bimolecular termination) [Figure 16]. These reactions mean that cationic polymerisation is not usually living.

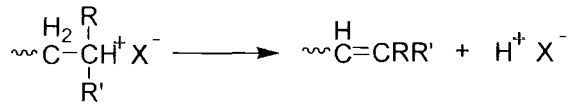


Figure 15 Unimolecular cationic termination

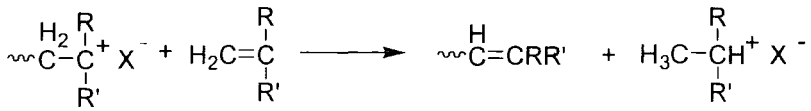


Figure 16 Bimolecular cationic termination

Despite these potential termination processes cationic polymerisation can be 'living' in systems in which the carbenium propagating ion is a sufficiently stable species. Anionic polymerisations may be initiated by either an anionic species or an alkali metal which can participate in an electron transfer to monomer. Each initiating species initiates one propagating polymer chain creating an anionic end group which then propagates through addition of vinyl monomer with regeneration of the active end group [Figure 17].

Figure 17 Anionic addition polymerisation

Anionic polymerisation is living as the absence of any termination reactions means that a propagating chain end will add monomer until it is completely consumed. Termination may occur, however, through the reaction of the propagating chain end with either trace impurities or water. Polymerisations exhausted of monomer may be restarted upon addition of either the original or a new monomer allowing chain extension or block copolymer synthesis.

The application of ionic polymerisation to vinyl species is not however general as the monomer functionalities dictate whether anionic and cationic addition polymerisation may be used. Anionic polymerisations generally require electron withdrawing substituents adjacent to the active centre in order to stabilise the propagating carbanion, similarly cationic polymerisations require electron donating substituents in order to stabilise the carbocationic propagating head group. In both anionic and cationic polymerisation rigorous attention must be paid to monomer and solvent purity as small levels of impurities or water would quickly terminate polymerisation leading to reduced molecular weight and the formation of dead

polymer. The choice of counterion is hugely important for the success of polymerisation as a consequence of the intimate association of counterion with the propagating chain end. Copolymerisations in which monomer units are distributed throughout the backbone are frequently impossible, as a result of the selectivity of ionic reactions to the electronic structure of monomer meaning that one monomer is largely preferred over the other until it is exhausted.

Subsequent introduction of different monomer into the polymerisation can be used to generate block copolymer species as the active species is conserved even at high conversion.

Controlled Radical Polymerisation

Otsu *et al.*[2] suggested that the radical polymerisation of vinyl monomers in homogenous solution might be carried out in a living fashion through the reversible capping of propagating radical chain ends by a stable radical species, such as the trimethyl phenyl radical, which would not in itself initiate new chains allowing a more synthetically straightforward route to tailored macromolecular architectures. A reaction scheme for this living radical polymerisation was suggested [Figure 18].

[2] Otsu, T., Yoshida, M., Tazaki, T., Macromolecular Chemistry Rapid Communications, **1982**, 3, 133-140

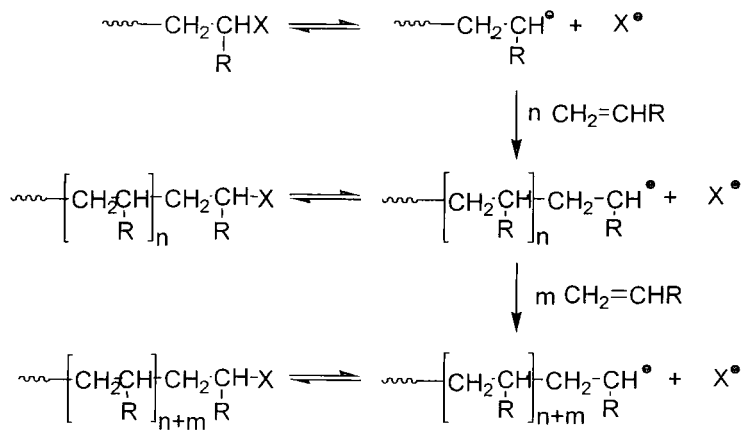


Figure 18 Otzu *et al.*[2] proposed mechanism for living radical polymerisation

This was proposed as resulting in a "pseudo-living" process which would behave in a similar fashion to living polymerisation with a linear increase in molecular weight with time and conversion and after cessation of initial polymerisation to be capable of undergoing subsequent chain extension on addition of fresh monomer.

This concept of living polymerisation via reversible end capping was developed from a previous paper from Otsu *et al.* [3] in which the end functionalisation of polymers prepared via free radical polymerisations was attempted using initiators prone to primary radical termination or with high transfer reactivity. These initiators were described as inifer (initiation transfer) or initer (initiation termination) reagents. Since the effects of these two processes are difficult to distinguish from each other the term iniferter (initiator transfer agent terminator) was coined to describe these reagents.

Triphenyl azomethane was used as a monofunctional iniferter resulted to produce α-phenyl ω-trityl polymers [Figure 19].

[3] Otsu, T., Yoshida, M., Macromolecular Chemistry Rapid Communications, **1982**, 3, 127-132

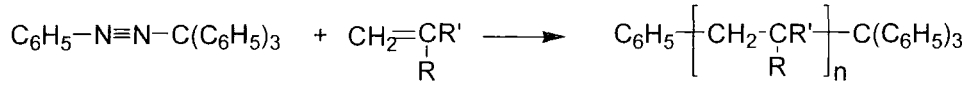


Figure 19 α-phenyl ω-trityl polymer

From reference to a previous study[4] in which it was shown that in the initial stages of polymerisation of methyl methacrylate initiated by 1,1,2,2-tetraphenyl-1,2-diphenoxy ethane a telechelic oligomer [Figure 20] is produced which was capable of initiating further polymerisation. It was realised that this ω-trityl functional polymer might be capable of dissociation to regenerate the radical chain end and undergo further polymerisation.

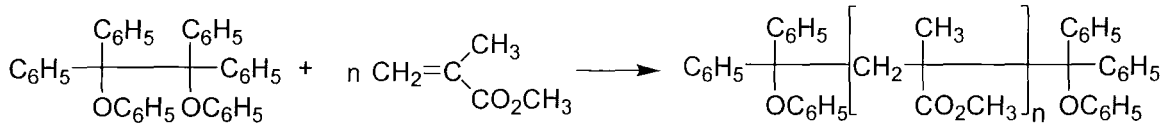


Figure 20 Telechelic oligo methyl methacrylate initiator

The ω-trityl polymers prepared by Otsu *et al.* were shown to be capable of thermal dissociation under the polymerisation conditions to regenerate a radical chain end capable of further propagataion. In polymerisation a linear growth in molecular weight with time or conversion was demonstrated similar to that observed in living polymerisations.

The use of S-benzyl-N,N-dimethyldithiocarbamate was also demonstrated as a photoiniferter [Figure 21] with which a similar growth in molecular weight with time or conversion and the ability to initiate further polymerisation was observed.

Figure 21 S-benzyl-N,N-dimethyldithiocarbamate photoiniferter living polymerisation

This photoiniferter was, however, shown to have several side reactions complicating the reaction scheme including the decomposition of the dithiocarbamate and

[4] Braun, D., Bledzki, A., Makromol. Chem, **1981**, 182, 1047-1056

formation of head to head terminated polymer and dithiocarbamate radicals via degenerative transfer, which may slowly initiate polymerisation.

Proposed Mechanisms for Radical End Capping

Since the early work of Otsu *et al.* a variety of reversible capping mediating systems have been subject to study the most extensively applied of which are atom transfer radical polymerisation, ATRP; reversible addition fragmentation polymerisation, RAFT; and nitroxide mediated polymerisation, NMP.

Atom Transfer Radical Polymerisation

ATRP[5] utilises a ligand complexed transition metal halide in conjunction with a conventional initiator. The transition metal centre can undergo a one electron reduction with an alkyl radical with donation of the halide atom to cap the radical. The corresponding oxidation of the metal centre by alkyl halide reverses this process regenerating the radical. Each initiation or propagation cycle consists of an atom transfer equilibrium and addition of the intermediate radical to monomer [Figure 22].

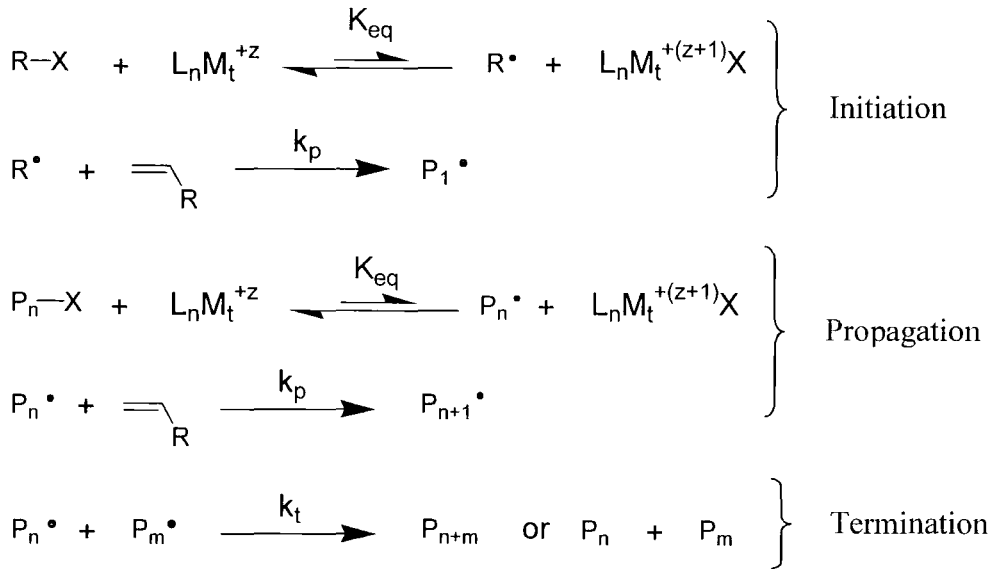


Figure 22 Atom transfer radical polymerisation

[5] Patten, T., Matyjaszewski, K., Adv. Mater., **1998**, 10, 12, 901-915

Reversible Addition Fragmentation Polymerisation

RAFT[6], sometimes referred to as degenerative chain transfer polymerisation utilises a transfer agent that can react with an initiating or propagating radical to regenerate a transfer agent and propagating radical via an exchange mechanism [Figure 23].

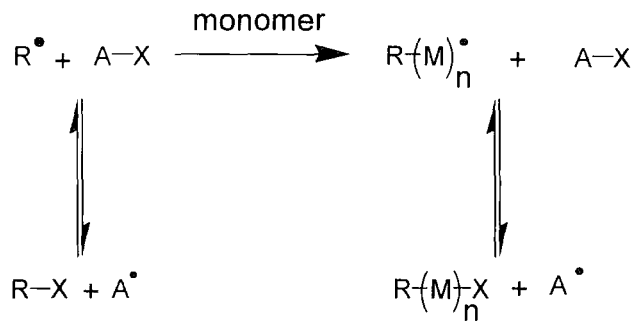


Figure 23 RAFT mechanism

Species such as dithioesters have been extensively studied as RAFT agents [Figure 24]

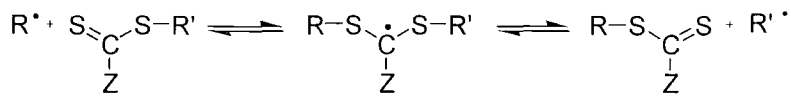


Figure 24 Reversible chain transfer utilising dithioester

These transfer species have been used to synthesise polymers with a linear increase in molecular weight growth with time and conversion, predicable molecular weight and narrow polydispersity. The dithioester terminated product polymer has been shown to be capable of further chain extension.

[6] Chiefari, J., Chong, Y.K., Ercole, F., Krstina, J., Jeffery, J., Le, T.P.T., Mayadunne, R.T.A., Meijs, G.F., Moad, C.L., Moad, G., Rizzardo, E., Thang, S.H., Macromolecules **1998**, 31, 5559-5562

Reversible Capping by Nitroxide

Stable nitroxide radicals have been utilised by chemists for some time; the inorganic nitroxide Fremy's salt, $(KSO_3)_2NO^{\cdot}$, has been known since 1845 while the first stable organic nitroxide was isolated in 1901. The reaction of stable nitroxides radicals with transient alkyl radicals to form an alkoxyamine has been extensively used in the trapping of radical intermediates in kinetic and mechanistic studies and as a general radical trap in the inhibition of polymerisation and the stabilisation of polymers and hydrocarbons to oxidative degradation.

An anomalous reaction order was noted by Howard and Tait[7] in the disappearance of the nitroxide during studies in to the production of 1,1-diphenyl ethane radical from the thermolysis of 2,2,3,3-tetraphenyl butane [Figure 25] utilising the loss in ESR signal of a 2,2,6,6-tetramethyl-4-oxopiperidinyl-1-oxyl, oxy-TEMPO nitroxide radical trap [Figure 26] to monitor alkyl radical production.

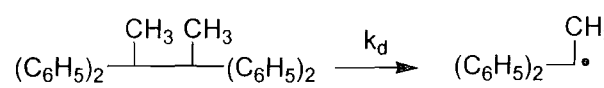


Figure 25 2,2,3,3 tetraphenyl butane homolysis

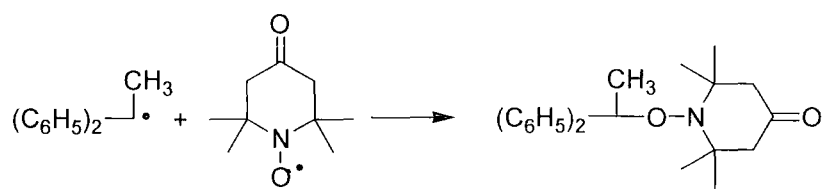


Figure 26 Trapping of 1,1-diphenyl ethane radicals with nitroxide

Despite the presence of a large excess in the alkyl radical producing species a low background concentration of free nitroxide was detected, the level of which could be raised or lowered reversibly through variation in temperature of the solution. It was proposed that the nitroxide trapping reaction was reversible with the alkoxyamine

[7] Howard, J.A., Tait, J.C., J. Org. Chem., **1978**, 43, 22, 4279-4283

product able to undergo thermal homolysis to regenerate nitroxide and carbon centred radicals [Figure 27].

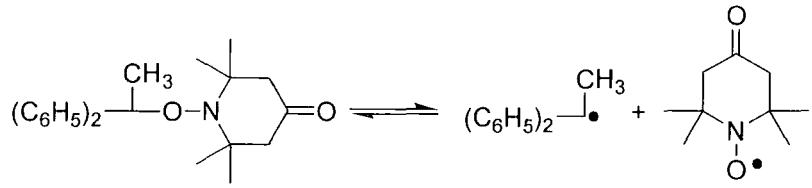


Figure 27 Reversible trapping of 1,1'-diphenyl ethane radical with oxy-TEMPO nitroxide

Heating of the isolated alkoxyamine in degassed deuterated chloroform or toluene was observed to result in the formation of a 4-oxo-TEMPO hydroxylamine and 1,1 diphenylethene [Figure 28].

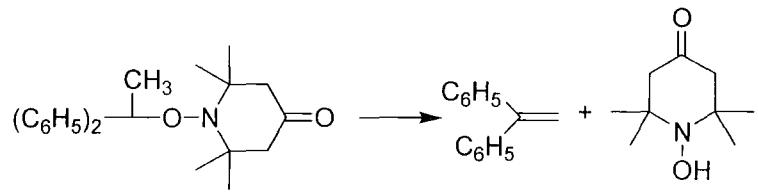


Figure 28 Formation of hydroxylamine and alkene in degassed chloroform and toluene

In the presence of oxygen nearly 100% yields of nitroxide were obtained along with acetophenone, benzophenone and 1,1 diphenyl ethane and a reaction scheme was proposed taking these observations into account [Figure 29].

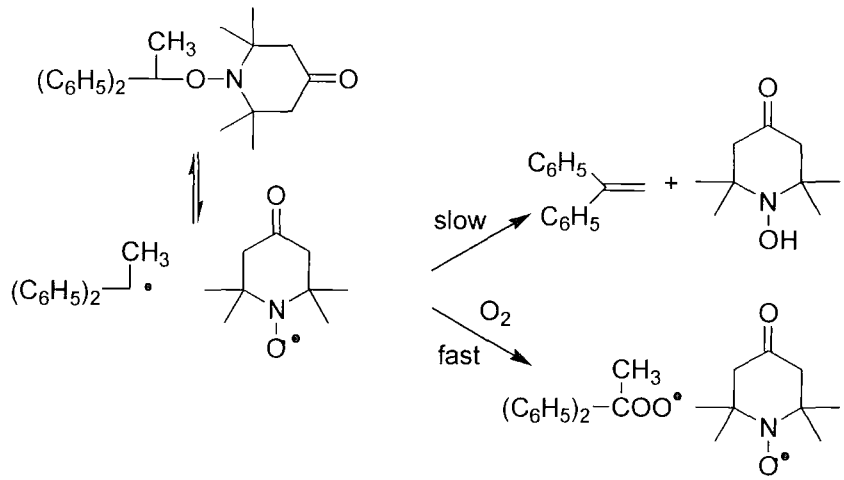


Figure 29 Proposed reaction scheme for reversible capping by nitroxide and side reaction

The formation of 1,1-diphenyl ethyl peroxyl in the presence of oxygen was confirmed by addition of a 2,6 di-*tert*-butyl-4-methyl phenol hydrogen atom donor [Figure 30] to the solution which resulted in the formation of products suggesting the trapping by oxygen of carbon centred radicals.

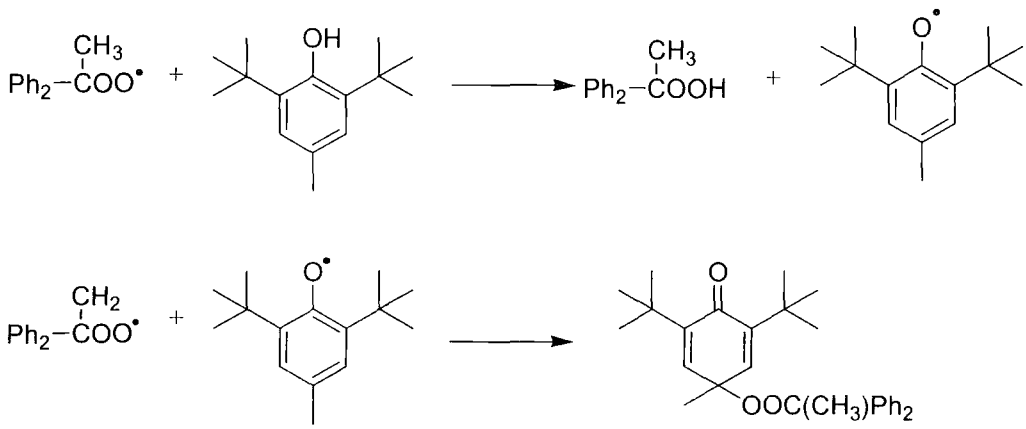


Figure 30 Proposed reaction scheme with added 2,6 di-*tert*-butyl-4-methylphenol

The decomposition of alkoxyamines based on 2,2,6,6-tetramethyl-4-oxopiperidinyl-1-oxy [Figure 31] was further studied by Grattan *et al.*[8] in both degassed solution and

[8] Grattan, D.W., Carlsson, D.J., Howard, J.A., Wiles, D.M., Can. J. Chem., **1979**, 57, 2834-2842

in the presence of dissolved atmospheric oxygen or added 2-methyl-2-nitrosopropane as alkyl radical traps.

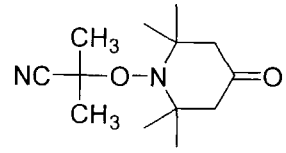


Figure 31 AIBN adduct of 4-oxy TEMPO nitroxide

This work further reinforced the suggestion that alkoxyamines produced by trapping of an alkyl radical by a nitroxide could undergo homolysis to regenerate the original radical species. As previously observed the homolysis products of an alkoxyamine species in the presence of a radical trap were the free nitroxide and trapping products of an alkyl radical. In the absence of a trapping agent the dominant products detected were hydroxylamine and alkene in agreement with the reaction scheme previously proposed.

Moad *et al.*[9] noted this reversibility of radical trapping of propagating radicals by nitroxides under thermal polymerisation conditions as part of a study into the trapping by TEMPO nitroxide of styrenic radicals formed reaction of primary initiating radicals with styrene monomer.

The use of nitroxides was subsequently patented by Rizzardo *et al.*[10] as a means of reversibly capping the radical polymerisation of olefinic monomers [Figure 32].

[9] Moad, G., Rizzardo, E., Solomon, D.H., Macromolecules, **1982**, 15, 909-914

[10] Solomon, D.H., Rizzardo, E., Cacioli, P., EP0135280, US 4,581,429

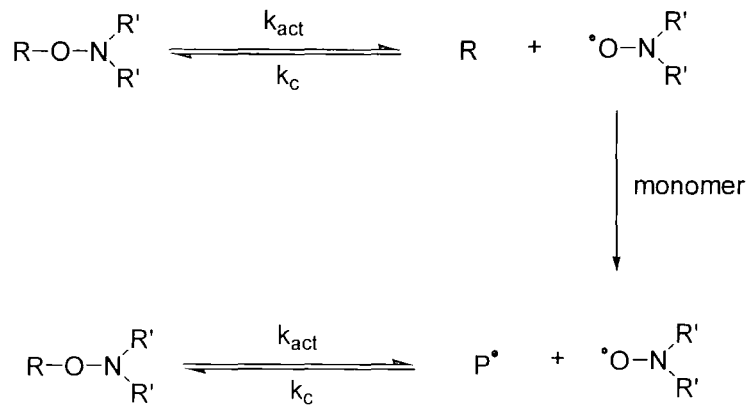


Figure 32 Rizzardo *et al.*[10] patented process for nitroxide mediated controlled radical polymerisation

The patent claims cover both the use of nitroxides to mediate polymerisation either in conjunction with a conventional initiating species or as a unimolecular initiating alkoxyamine species and describes the synthesis of varied macromolecular structures including copolymers, block copolymers and graft copolymers based on this process. This approach to the control of radical polymerisation has led to a number of studies in which the understanding of the elementary reactions in controlled radical polymerisation; radical trapping, alkoxyamine homolysis and alkene/hydroxylamine formation has developed in parallel with broader work on the kinetics, mechanism and application of controlled radical polymerisation.

Radical Trapping by Nitroxide

The trapping by stable nitroxide radicals of transient alkyl radicals used in a variety of applications had for some time been largely presumed to be diffusion limited. In order to test this assumption measurement was carried out[11] of the rate of reaction of tetramethylisoindole-2-oxyl nitroxide radical [Figure 33] with "radical clock" alkyl

[11] Beckwith, A.L.J., Bowry, V.W., O'Leary, M., Moad, G., Rizzardo, E., Solomon, D.H., J. Chem. Soc. Chem. Commun., **1986**, 1003-1004

radicals species which undergo a well characterised cyclisation reaction allowing determination of the rate constant for coupling with nitroxide [Figure 34].

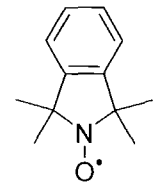


Figure 33 Tetramethylisoindole-2-oxyl nitroxide

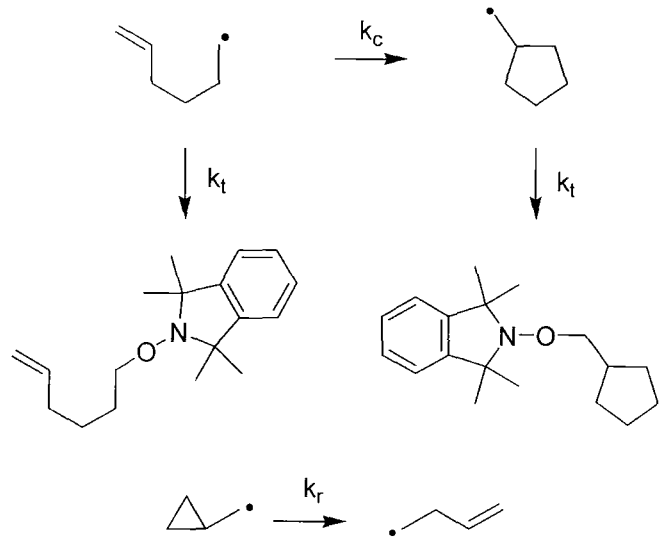


Figure 34 Radical cyclisation clock reactions

Analysis by reverse phase high performance liquid chromatography of the products of trapping competition studies allowed calculation of the rates of nitroxide trapping which were an order of magnitude lower than those rate constants expected for the reaction under diffusion control.

Subsequent studies by Ingold *et al.* [12] using similar radical clock methods investigated the kinetics of tetramethyl isoindole-2-oxyl nitroxide radical trapping in solvents of varying polarity. The results obtained suggest a significant influence of solvent polarity on the rate of trapping, it being slowed with increasing solvent

[12] Beckwith, A.L.J., Bowry, V.W., Ingold, K.U., J. Am. Chem. Soc., **1992**, 114, 13, 4983-4992

polarity. This solvent polarity effect was ascribed to differences in the free energy of solvation between the reactants and the transition state. The difference in solvation energy between the carbon radical and the product alkoxyamine hydrocarbon portion was not considered as being significant however it was suggested that strong solvation of the free nitroxide is possible in polar, polarizable and solvents capable of participating in hydrogen bonding. This is suggested to be due to the substantial dipole moment which results from the canonical forms of the nitroxide [Figure 35] each of which make approximately equal contributions to the electron distribution.

Figure 35 Nitroxide canonical forms

Supplementary evidence for this proposition is available from studies on the ESR spectra which suggest that the dipolar resonance form is favoured in polar solvents. A plot of $\log((k_t/k_c/M^{-1})$ against the 4-amino TEMPO nitroxide hyperfine splitting in solvents of varying polarity results in a linear relationship with a deviation from this in solvents capable of participating in hydrogen bonding. It was also suggested that where the nitroxide is strongly solvated it becomes more difficult for an alkyl radical to displace solvent and react with the nitroxide. The rates of radical trapping in water and alcohols were observed to be anomalously lower than those expected solely as a consequence of solvent polarity. This was ascribed to a result of the formation of hydrogen bonds with the nitroxide, further enhancing the dipolar form.

Further studies were carried out by the same workers[13] using kinetic competition product and laser flash photolysis experiments, into the effect of nitroxide structure comparing the rates of trapping of alkyl radicals by 2,2,6,6-tetramethylpiperidine-N-

[13] Bowry, V.W., Ingold, K.U., J. Am. Chem. Soc., **1992**, 114, 4992-4996

oxyl (TEMPO), 1,1,3,3-tetramethyl isoindoline-2-oxyl (TMIO), di-*tert*-butyl nitroxide DTBN, 9-azabicyclo[3.3.1]nonane-N-oxyl (ABNO) and nortropane-N-oxyl (NTNO) nitroxides [Figure 36].

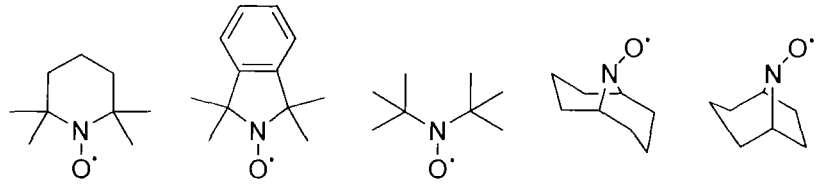


Figure 36 TEMPO, TMIO, DBNO, ABNO and NTNO nitroxides

The steric hinderance around the nitroxide functionality was shown to affect the rate of nitroxide trapping of carbon centred radicals. The fastest trapping rates were observed with ABNO and NTNO nitroxides with decreased rates for cyclic systems in order from five to six membered rings and still further to open chain species. The rate of nitroxide trapping was further reduced with resonance stabilised or sterically protected carbon centred radicals.

Studies by Scaiano *et al.*[14] into the trapping reaction of nitroxides [Figure 37] using laser flash photolysis of various alkoxyamines. This showed that the rates of trapping were slowest with the bulky di-*tert*-butyl nitroxide radical and resonance or sterically stabilised alkyl radicals.

[14]Skene, W.G., Scaiano, J.C., Listigovers, P.M., Georges, M.K., Macromolecules, **2000**, 33, 5056-5072

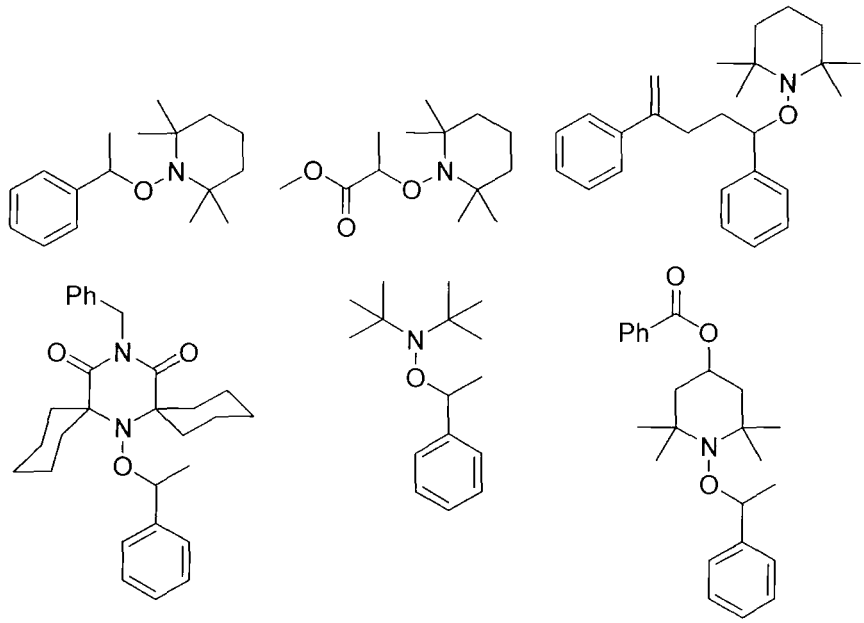


Figure 37 Alkoxyamines studied by Scaiano[14]

Fischer and coworkers carried out a contemporary laser flash photolysis study[15] into trapping by several nitroxides [Figure 38] of the methoxycarbonyl isopropyl and methoxycarbonyl methyl radicals [Figure 39].

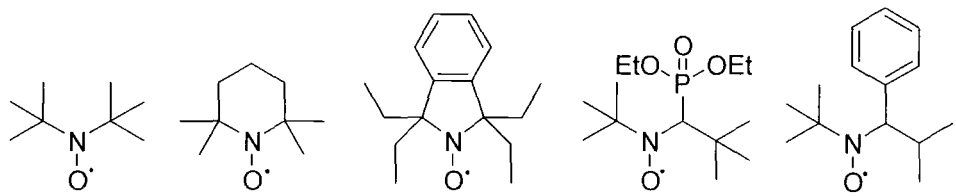


Figure 38 DBNO, TEMPO, TEIO, SG1 and TIPNO nitroxides studied by Fischer *et al.*[15]

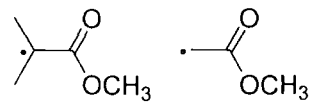


Figure 39 Methoxycarbonyl isopropyl and methoxycarbonyl methyl radicals

The rate constants for the trapping reaction were found to depend strongly on the steric hinderance around the nitroxide functional group. Upon moving from TEMPO and TEIO to the open chain nitroxides with α-hydrogen substituents and increased

[15] Sobek, J., Martschke, R., Fischer, H., J. Inf. Recording, **2000**, 25, 455-463

steric shielding of the nitroxide radical, the trapping rate constants were shown to vary by two orders of magnitude. This study also confirmed the rate dependence due to shielding of the alkyl radical observed previously.

Alkoxyamine Homolysis

Moad and Rizzardo[16] examined the factors influencing the rate of alkoxyamine carbon to oxygen bond homolysis through determination by HPLC of the alkoxyamine half-lives under irreversible conditions in the presence of an excess of dissimilar nitroxide trapping species to remove transient radical products and prevent the trapping back reaction. This allowed the calculation of half lives of a series of alkoxyamines formed from several nitroxides [Figure 40] with different alkyl residues.

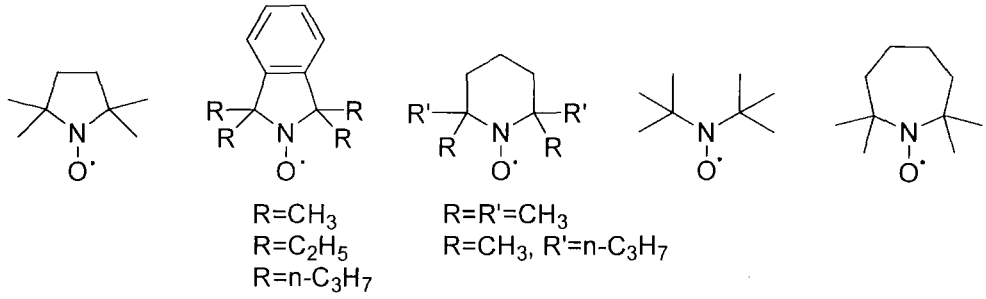


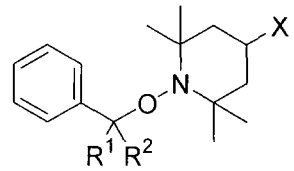
Figure 40 Nitroxides used by Moad and Rizzardo[16]

These experiments showed an increase in alkoxyamine homolysis rates with increased steric crowding of the nitroxide, increasing progressively with ring size to open chain and with larger alkyl substituents adjacent to the nitroxide functional group. Increasing homolysis rates were also observed with increasing solvent polarity. Homolysis rates were found to be related to the structure of the leaving radical although the relative effects of steric bulk and electronic structure were

[16] Moad, G., Rizzardo, E., Macromolecules, **1995**, 28, 8722-8728

difficult to separate. Calculations of alkoxyamine properties by semi-empirical molecular orbital method were shown to agree with experimental trends.

Scaiano *et al.*[17] carried out a study using a similar approach to that of Moad and Rizzardo of alkoxyamine homolysis in the presence of an excess of a dissimilar trapping nitroxide and HPLC of the products. This work confirmed the earlier findings of Moad and Rizzardo observing an increase in homolysis rate with increasing steric hinderance of benzylic radicals when TEMPO and hydroxy TEMPO were used as nitroxides fragments [Figure 41].



R^1=R^2=X=H
R^1=X=H; R^2=CH_3
R^1=R^2=CH_3; X=H
R^1=R^2=H; X=OH

Figure 41 TEMPO and hydroxy TEMPO alkoxyamines studied by Scaiano[17]

Semi-empirical molecular orbital calculations of alkoxyamine bond strength carried out by Kazmaier *et al.*[18] the noted trends in bond strengths showing broad agreement with data obtained experimentally. The calculation of alkoxyamine carbon to oxygen bond dissociation energy was extended further by de Sainte Claire *et al.*[19] using density functional theory to achieve better correlation with experimental studies.

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[17] Skene, W.G., Belt, S.T., Connolly, T.J., Hahn, P., Scaiano, J.C., Macromolecules, **1998**, 31, 9103-9105

[18] Kazmaier, P.M., Moffat, K.A., Georges, M.K., Veregin, R.P.N., Hamer, G.K., Macromolecules **1995**, 28, 1841-1846

[19] Marsal, P., Roche, M., Tordo, P., de Sainte Claire, P., J. Phys. Chem. A, **1999**, 103, 2899-2905

Fischer *et al.*[20] used a quantitative ESR measurement technique to study the rate of nitroxide formation from alkoxyamine homolysis in the presence of excess trapping species, either oxygen, galvinoxyl or labelled nitroxide, comparing the homolysis of a series of twenty seven alkoxyamines based on six nitroxides [Figure 42] with different carbon centred radical fragments [Figure 43]. Construction of an Arrhenius plot from the alkoxyamine homolysis rates measured at several temperatures allowed calculation of the alkoxyamine bond strengths. The bond strengths calculated are in some cases slightly different to those obtained by other groups, the differences were ascribed to an error compensation effect in data analysis. An average pre-exponential factor was obtained and used to calculated bond dissociation enthalpies for a number of further alkoxyamines.

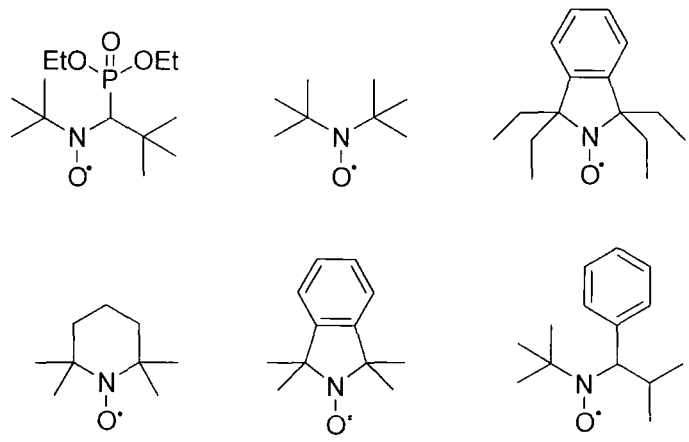

Figure 42 Nitroxides studied by Fischer *et al.*[20]

[20] Marque, S., Le Mercier, C., Tordo, P., Fischer, H., Macromolecules, **2000**, 33, 12, 4403-4410

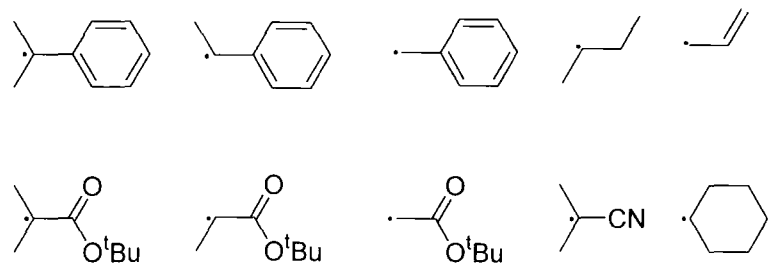

Figure 43 Carbon centred radicals studied by Fischer *et al.*[20]

The alkoxyamine carbon to oxygen bond strength was shown to be related to the alkane carbon to hydrogen bond strength corresponding to the leaving radical in agreement with a previous study by Mulder *et al.*[21] in which a relationship was noted between the alkoxyamine bond enthalpy and alkane carbon to hydrogen bond enthalpy by photoacoustic calorimetry although with far fewer data points. The activation energy was shown to decrease with the steric bulk of alkoxyamine nitroxide group in accordance with the earlier observations of Moad and Rizzardo.

Further study by Fischer *et al.*[22] using quantitative ESR of alkoxyamine homolysis under irreversible conditions with an excess of a trapping species confirmed the previously proposed correlation between alkane carbon to hydrogen bond strength and alkoxyamine carbon to oxygen bond strength. The effect of polar and protic solvents in increasing alkoxyamine homolysis rate observed by Moad and Rizzardo was also reproduced. With this solvent influence in mind a group of alkoxyamines [Figure 44] was synthesised to investigate the effects of nitroxide intramolecular hydrogen bonding on alkoxyamine bond homolysis with tethered or non hydrogen bonding analogues synthesised in order to distinguish between hydrogen bonding and steric influences. These studies suggested that the alkoxyamines derived from

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[21] Ciriano, M.V., Korth, H., van Scheppingen, W.B., Mulder, P., J. Am. Chem. Soc. **1999**, 121, 6375-6381

[22] Marque, S., Fischer, H., Baier, E., Studer, A., J. Org. Chem., **2001**, 66, 4, 1146-1156

nitroxides able to participate in intramolecular hydrogen bonding [Figure 45] have significantly increased rates of alkoxyamine dissociation.

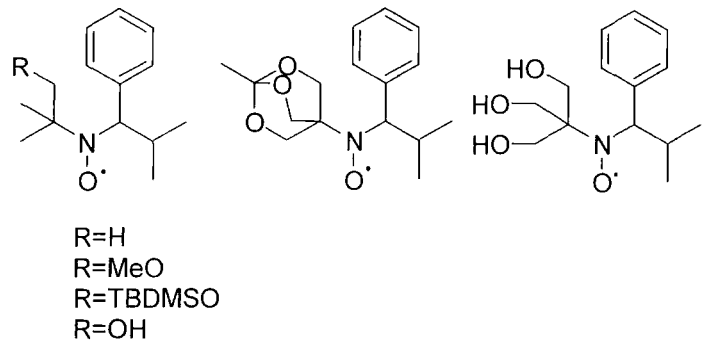

Figure 44 Nitroxides studied by Fischer *et al.*[22]

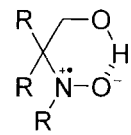

Figure 45 Intramolecular hydrogen bonding

Studies by a number of groups into the alkoxyamine bond homolysis of polymeric alkoxyamines have produced conflicting results. German *et al.*[23] measured the rate of alkoxyamine homolysis by quantitative ESR studies on nitroxide evolution in the presence of dissolved oxygen as a trapping species reporting a larger homolysis rate of polymeric TEMPO adduct than that of the comparable small molecule species, this difference was largely ascribed to entropic effects resulting from increased steric strain in the polymer adduct.

Fukuda and Goto[24] used a GPC resolution method, looking at the GPC trace of polymeric alkoxyamine adducts over time allowing separation of the initiating adduct from those chains which had undergone activation and propagation, in order to calculate the rate of activation. Fukuda calculated alkoxyamine bond dissociation

[23] Bon, S.A.F., Chambard, G., German, A.L., Macromolecules, **1999**, 32, 8269-8276

[24] Goto, A., Fukuda, T., Macromol. Chem. Phys., **2000**, 201, 2138-2142

rates for polymeric alkoxyamines based on TEMPO, DBN and DEPN nitroxides two to three fold higher than those previously calculated by Fischer for the comparable small molecule alkoxyamines. Gnanou *et al.*[25], however, using the same GPC approach to that of Fukuda obtained Arrhenius parameters for the DEPN nitroxide based polymeric alkoxyamine almost identical to that of the low molecular weight alkoxyamine. Tordo *et al.*[26] noting the disparate literature reports studied the effect of polymeric chain length on SG1 nitroxide alkoxyamine homolysis by quantitative ESR studies from which no clear influence of the chain length on the rate of dissociation could be discerned.

Role of Hydrogen Abstraction Decomposition

Initial studies into the thermal stability of alkoxyamines noted a hydrogen transfer disproportionation reaction competing with nitroxide trapping resulting in the formation of hydroxylamine and an unsaturated species.

Studies were carried out by Priddy *et al.*[27] using HPLC and ^{1}H NMR spectroscopy into the thermal decomposition of the styryl TEMPO alkoxyamine adduct [Figure 46].

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[25] Benoit, D., Grimaldi, S., Robin, S., Finet, J-P., Tordo, P., Gnanou, Y., J. Am. Chem. Soc., **2000**, 122, 5929-5939

[26] Bertin, D., Chauvin, F., Marque, S., Tordo, P., Macromolecules, **2002**, 35, 10, 3790-3791

[27] Li, I., Howell, B.A., Matyjaszewski, K., Shigemoto, T., Smith, P.B., Priddy, D.B., Macromolecules **1995**, 28, 6692-6693

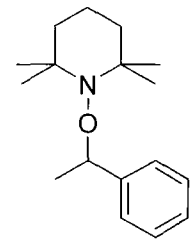

Figure 46 Styryl TEMPO adduct alkoxyamine

This study showed a decomposition reaction as previously observed which operates in competition with the activation/deactivation reversible reaction resulting in the formation of styrene. A mechanism was proposed in which in-cage abstraction of the hydrogen β to the alkyl radical occurs with formation of styrene and hydroxylamine [Figure 47].

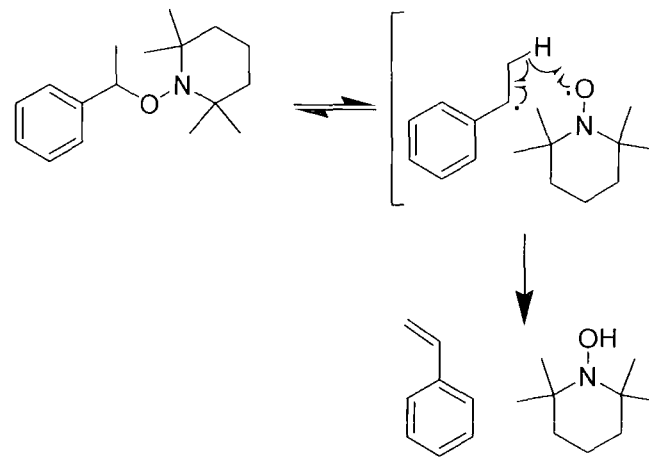

Figure 47 Mechanism proposed by Priddy[27] for β-hydrogen transfer disproportionation

This hydrogen transfer disproportionation decomposition was suggested as potentially being a significant cause of termination of the growing polymer chains and hence polydispersity broadening.

Work by Gridnev[28] examined the further role of the hydroxylamine product formed by this decomposition reaction. Addition of hydroxylamine to a polymerisation

[28] Gridnev, A.A., Macromolecules, **1997**, 30, 7651-7654

medium resulted in the observation of an induction period for the polymerisation and reduced the subsequent rate of polymerisation. This was suggested to be due to re-oxidation of the hydroxylamine to nitroxide by alkyl radicals with corresponding reduction of the alkyl radical [Figure 48]. It was suggested that the hydroxylamine decomposition product acts as catalytic chain termination agents.

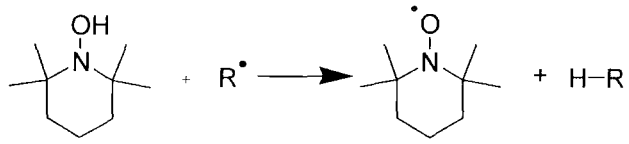

Figure 48 Oxidation of hydroxylamine by carbon centred radical

Fukuda *et al.*[29] carried out further studies into the kinetics of hydrogen transfer disproportionation decomposition comparing small molecules and polymeric TEMPO alkoxyamines [Figure 49] in an attempt to study the prevalence of decomposition in polymerisation.

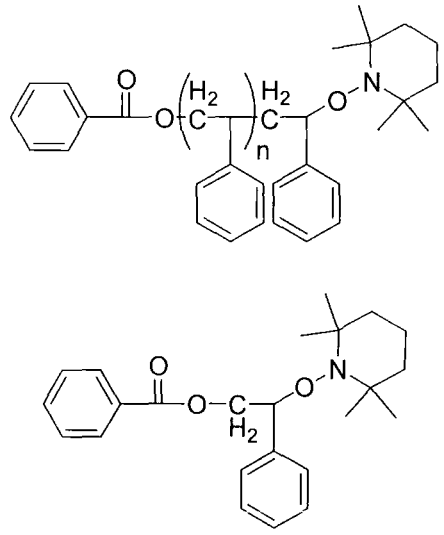

Figure 49 PS-TEMPO and BS-TEMPO polymeric and unimolecular adducts

The hydrogen transfer disproportionation decomposition of both the BS and PS TEMPO alkoxyamines were observed to be markedly less significant than that

[29] Ohno, K., Tsujii, Y., Fukuda, T., Macromolecules, **1997**, 30, 2503-2506

previously observed by Li *et al.* for styryl TEMPO alkoxyamine. This reduction in hydrogen transfer disproportionation decomposition of PS and BS alkoxyamines was greater than that which might be expected simply as a consequence of the reduced number of available β-hydrogens. It was suggested that steric factors resulting from the substitution of the styryl residue might result in an unfavourable conformational preference for the decomposition to occur.

A study by Scaiano *et al.*[30] into a TEMPO alkoxyamine containing the penultimate polystyryl [Figure 50] unit as a potential initiator similarly showed a significant reduction in the level of hydrogen transfer disproportionation decomposition.

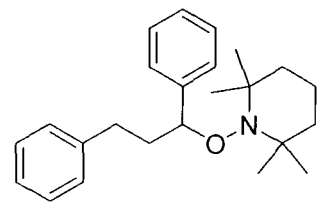

Figure 50 Penultimate styryl unit alkoxyamine

This was rationalised on steric grounds describing the hydrogen transfer disproportionation decomposition as a four centre elimination reaction requiring a syn-periplanar conformation of the H-C-C-O moiety. This conformation is readily accessible for the styryl TEMPO alkoxyamine, however the alkoxyamine with the penultimate styrene unit alkoxyamine was shown to have a preferred staggered conformation with the CH_2-Ph group anti-periplanar with respect to the nitroxide oxygen and suggested to hence greatly reduce the level of disproportionation. Studies by Fukuda *et al.*[31] into the disproportionation rate of several alkoxyamines showed a decrease in disproportionation with increasing steric hindrance around the nitroxide

[30] Skene, W.G., Scaiano, J.C., Yap, G.P.A., Macromolecules, **2000**, 33, 3536-3542

[31] Goto, A., Kwak, Y., Yoshikawa, C., Tsujii, Y., Sugiura, Y., Fukuda, T., Macromolecules, **2002**, 35, 3520-3525

functionality and a reduced level of disproportionation in an alkoxyamine based on nitroxide capable of participating in intramolecular hydrogen bonding.

The influence on polymerisation kinetics of hydrogen abstraction decomposition has since been examined by Fischer *et al.*[32] resulting in predictions of conversion rates, upper conversion limits and "dead" polymer content in agreement with experimental observations. The effects on polymerisation kinetics of hydrogen transfer disproportionation were also modelled using Monte Carlo simulation by *Yang et al.*[33] The level of decomposition of several alkoxyamines with different alkyl segments have been studied by Fisher and Ananchenko[34]. This suggested that the level of hydrogen abstraction decomposition in growing polymer chains with more labile backbone hydrogens, such as methyl methacrylate, is a far more significant process than in polymerisation of styrene and related monomers with greater impact into the outcome of polymerisation

Nitroxide Mediated Radical Polymerisation

Subsequent to the patenting, by Rizzardo *et al.*, of the control of radical polymerisation through reversible capping by stable nitroxides it was several years before the next significant work in this field with Georges *et al.*[35] demonstrating the use of nitroxides for controlled radical polymerisation of styrene with TEMPO, 2,2,6,6 tetramethylpiperidine-N-oxyl [Figure 51], initiated by benzoyl peroxide. This

[32] Souaille, M., Fischer, H., Macromolecules, **2001**, 34, 2830-2838

[33] He, J., Li, L., Yang, Y., Macromolecules, **2000**, 33, 2286-2289

[34] Ananchenko, G.S., Fischer, H., Journal of Polymer Science: Part A: Polymer chemistry, **2001**, 39, 3604-3621

[35] Georges, M.K., Veregin, R.P.N., Kazmaier, P.M., Hamer, G.K., Macromolecules, **1993**, 26, 2987-2988

produced a polymer with low polydispersity, ~1.3, samples taken over the polymerisation showed increasing molecular weight with conversion which suggested a living process.

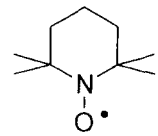

Figure 51 TEMPO radical

Subsequent work[36] using ESR spectroscopy to monitor the TEMPO nitroxide in the presence of a benzoyl peroxide initiator in toluene showed a reduction in the concentration of TEMPO with time. This was suggested to be a result of the induced decomposition of benzoyl peroxide by nitroxides, a redox reaction in which TEMPO is oxidised to a cation [Figure 52].

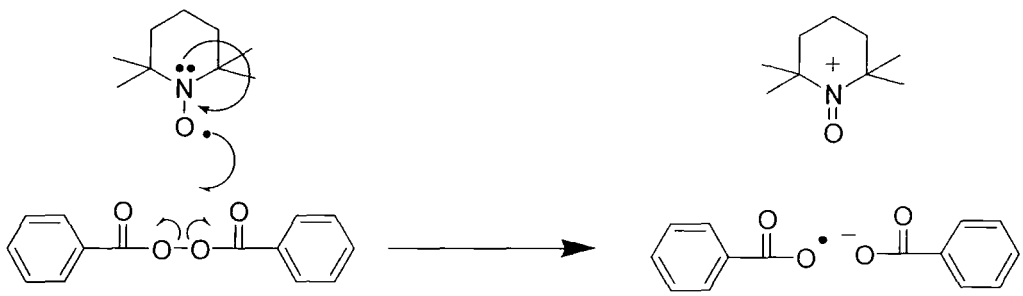

Figure 52 TEMPO induced decomposition of benzoyl peroxide

In the presence of styrene this free concentration of TEMPO was shown to be further reduced, presumably as a result of the capping by TEMPO of propagating radicals [Figure 53].

[36] Veregin, R.P.N., Georges, M.K., Kazmaier, P.M., and Hamer, G.K., Macromolecules, **1993**, 26, 5316-5320

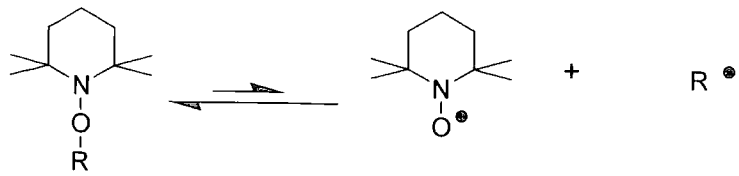

Figure 53 TEMPO capping of propagating radicals

Hawker[37] demonstrated the polymerisation of styrene initiated by an alkoxyamine species incorporating both initiating and mediating species as a presynthesised alkoxyamine [Figure 54] analogous to the terminal styrene unit of polystyrene. This alkoxyamine was prepared by the reaction of benzoyl peroxide with styrene in the presence of an excess of TEMPO nitroxide, isolated, purified and shown to be stable enough to be stored under normal lab conditions yet capable of initiating polymerisation via a thermal homolysis reaction generating a propagating radical and mediating nitroxide radical in stiochiometric quantities [Figure 55]. Similar to bimolecular initiation which uses free nitroxide in conjunction with a conventional initiator, a linear molecular weight growth with time was observed and low polydispersity material was obtained.

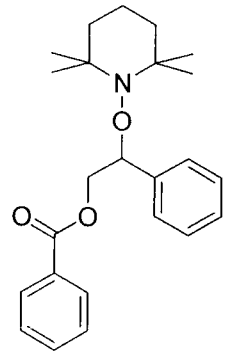

Figure 54 Hawker unimolecular initiator

[37] Hawker, C.J., J. Am. Chem. Soc., **1994**, 166, 11185-11186

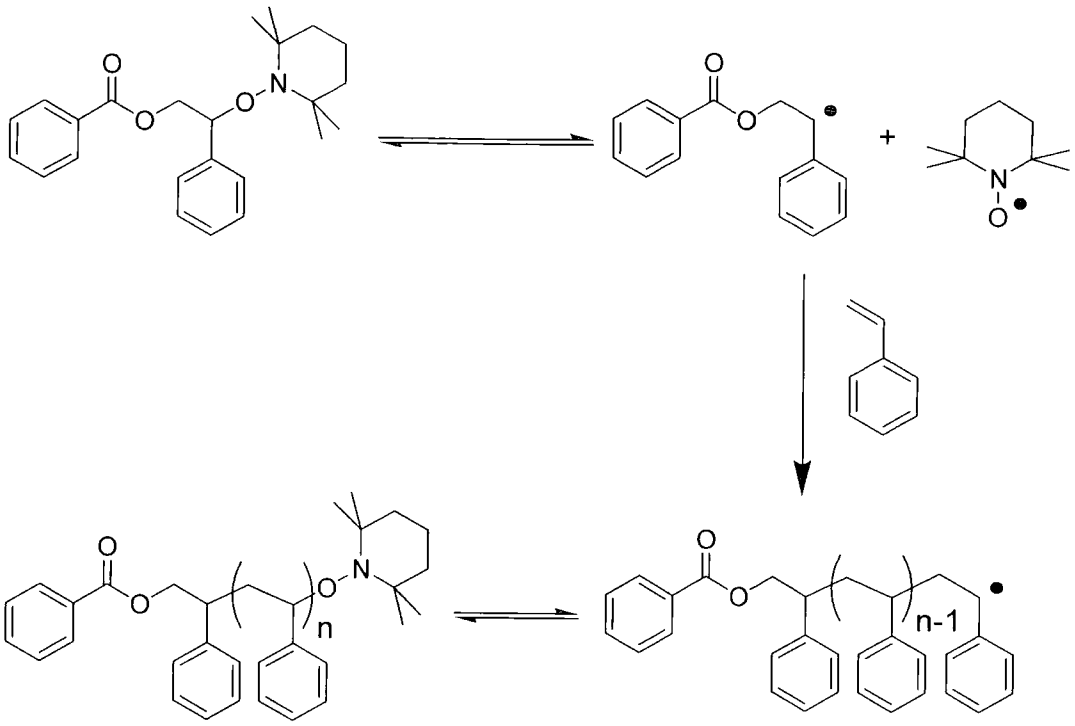

Figure 55 Unimolecular initiation of styrene polymerisation

The industrial utility of nitroxide controlled polymerisation was investigated by Saban *et al.*[38] demonstrating the absence of the gel, or Trommsdorf, effect in bulk polymerisation of styrene mediated by nitroxide. As initiation is rapid and termination controlled this suggests that industrial scale up of nitroxide mediated polymerisation should prove less problematic than conventional free radical polymerisation.

Hawker *et al.*[39] compared unimolecular initiator to bimolecular initiating systems showing that unimolecular initiation resulted in improved molecular weight and polydispersity control.

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[38] Saban, M.D., Georges, M.K., Veregin, R.P.N., Hamer, G.K., Kazmaier, P.M., Macromolecules, **1995**, 28, 7032-7034

[39] Hawker, C.J., Barclay, G.G., Orellana, A., Dao, J., Devonport, W., Macromolecules, **1996**, 29, 26, 5345-5254

Analysis of the polystyrene chain ends produced through unimolecular initiation was carried out by Hawker and Hedrick[40] which showed that a one to one ratio of initiating and mediating groups were incorporated into the polymer. In comparison bimolecular initiation with TEMPO in conjunction with benzoyl peroxide the initiating end groups in chain ends were shown to be poorly defined. This might be expected as previous investigation[41] of the reaction radicals derived from benzoyl peroxide with styrene in the presence of nitroxides has shown that the initiating radical resulting from homolysis of benzoyl peroxide is poorly defined with a variety of initiating radical species potentially being evolved. A crossover study was carried out by Hawker *et al.*[42] in order to establish whether nitroxides were efficiently exchanged between chain ends or were largely contained within the solvent cage. A statistical mix of products was obtained suggesting that the crossover of capping species is an efficient process and that complete homolysis of the alkoxyamine bond and separation of the radicals occurs.

The kinetics of styrene polymerisation in the presence of TEMPO and 3-carboxy-2,2,5,5 tetramethyl-1-pyrrolidinoxyl with benzoyl peroxide [Figure 56] were studied by Veregin *et al.*[43] and comparisons drawn with ESR studies into homolysis of model alkoxyamines [Figure 57]. Calculations were presented suggesting that irreversible termination occurred in approximately 1% of chains at 30,000 molecular weight and that the rate of polymerisation was determined by monomer propagation

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[40] Hawker, C.J., Hedrick, J.L., Macromolecules, **1995**, 28, 2993-2995

[41] Moad, G., Rizzardo, E., Solomon, D.H., Macromolecules, **1982**, 15, 909-914

[42] Hawker, C.J., Barclay, G.G., Dao, J., J. Am. Chem. Soc., **1996**, 118, 11467-11471

[43] Veregin, R.P.N., Georges, M.K., Hamer, G.K., Kazmaier, Macromolecules, **1995**, 28, 13, 4391-4398

rate constant and the equilibrium between the reversible capping and homolysis reactions.

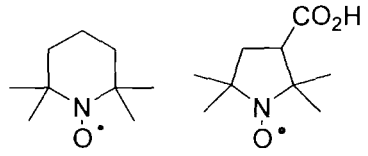

Figure 56 TEMPO and 3-carboxy-2,2,5,5 tetramethyl-1-pyrrolidinoxyl nitroxides

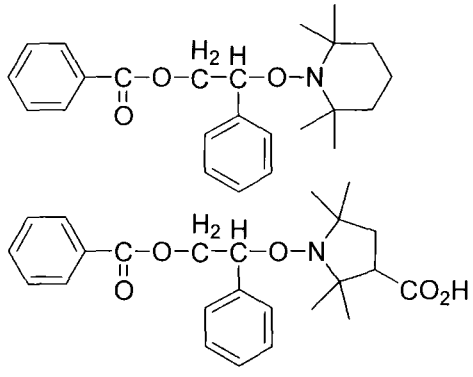

Figure 57 TEMPO and 3-carboxy-2,2,5,5 tetramethyl-1-pyrrolidinoxy model alkoxyamines

An examination of the optimal ratio of initiator to nitroxide by Veregin *et al.*[44] showed that the concentration of nitroxide must be equal to or greater than the concentration of propagating chains in order for polymerisation to proceed in a well controlled fashion. In bimolecular initiation it was observed that almost all of the initially free TEMPO is rapidly removed in capping alkyl radicals. As part of this study comment was made that that some feedback process appeared to be in operation which controlled the ratio of free nitroxide to growing chains. It was observed than increasing excess of nitroxide led to a reduction in polymerisation rate.

[44] Veregin, R.P.N., Odell, P.G., Michalak, L.M., Georges, M.K., Macromolecules, **1996**, 29, 2746-2754

The effect of varying the ratio of excess nitroxide to propagating chains was further investigated[45] with the conclusion that final conversion and product polydispersity were tuneable through the selection of suitable nitroxide to initiator ratios and that a self correcting buffering mechanism was in operation which adjusted the number of growing chains to maintain equilibrium with the free nitroxide. In polymerisations in which this ratio is too low irreversible termination occurs resulting in the formation of "dead" polymer chains until such point as a sufficient ratio of nitroxide to growing chains is re-established.

An investigation from Hawker *et al.*[46] into the autoinitiation of styrene in the presence of nitroxides was also shown to result in a controlled polymerisation. An incubation period was observed which was shown to be dependent on the nitroxide concentration consistent with radical trapping by nitroxide until this is exhausted after which propagation occurs. Analysis of the structures of nitroxide trapping products of initiators generated in-situ were shown to be consistent with the thermal autoinitiation of styrene via the mechanism described by Mayo[47] through a Diels Alder cyclisation between two monomer molecules and reaction of the subsequent dimer with styrene to generate radicals [Figure 58].

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[45] MacLeod, P.J., Vergin, R.P.N., Odell, P.G., Georges, M.K., Macromolecules, **1997**, 30, 2207-2208

[46] Devonport, W., Michalak, L., Malmström, E., Mate, M., Kurdi, B., Hawker, C.J., Barclay, G.G., Sinta, R., Macromolecules, **1997**, 30, 1929-1934

[47] Mayo, F.R., J. Am. Chem. Soc., **1968**, 90:5, 1289-1295

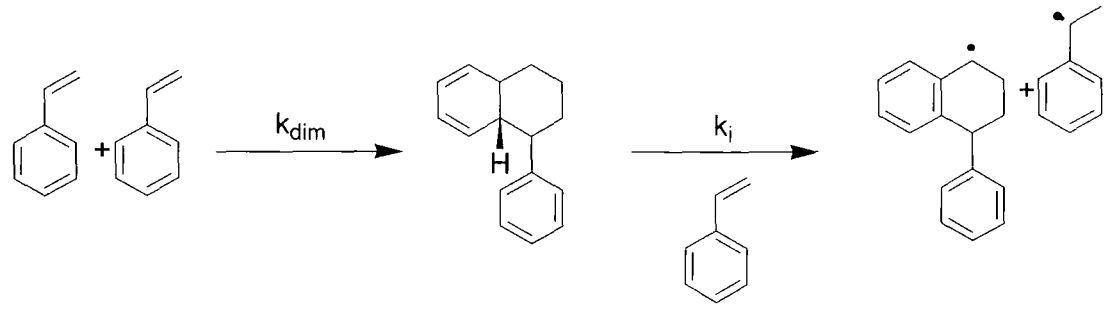

Figure 58 Mayo[47] mechanism for styrene autopolymerisation

Fukuda and Goto[48] studied the activation of an alkoxyamine terminated polystyrene adduct with styrene monomer in order to establish whether activation occurs solely via unimolecular homolysis or whether degenerative transfer also contributes [Figure 59].

$$P\text{–}X \underset{k_c}{\overset{k_d}{\rightleftharpoons}} P^{*} + X^{*}$$

$$P\text{–}X + P^{*} \overset{k_{ex}}{\rightleftharpoons} P^{*} + P\text{–}X$$

Figure 59 Unimolecular decomposition and degenerative transfer

The kinetics of activation were studied by a gel permeation chromatography resolution method which allowed separation of initiating polymeric adduct from those chains which had undergone activation and propagation allowing calculation of an activation frequency. In order to discern between uni and bimolecular activation the frequencies of activation were compared for polymeric adduct with and without added initiator. These activation frequencies were identical suggesting that rates of activation are independent of propagating radical concentration and therefore that any bimolecular activation is insignificant.

[48] Goto, A., Fukuda, T., Macromolecules, **1997**, 30, 5183-5186

Kinetics of Nitroxide Mediated Polymerisation

Kinetic equations derived by Muller[49] for the analysis of group transfer polymerisations were modified and applied by Veregin *et al.*[50] to nitroxide mediated polymerisations in order to predict chain length and polydispersities. Using suitably chosen rate constants for propagation, nitroxide trapping and alkoxyamine homolysis allowed calculation of product polydispersity and molecular weight reasonably fitting experimental observations.

The kinetics of nitroxide mediated polymerisation initiated by the unimolecular initiator styryl di-*tert*-butyl nitroxide [Figure 60] were investigated by Catala *et al.*[51] as a function of temperature and initiating adduct concentration.

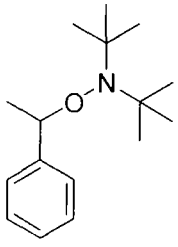

Figure 60 Styryl di-*tert*-butyl nitroxide

As might be expected an increase in polymerisation rate was observed with increasing temperature. An unusual result was, however, obtained in investigation into the dependence of polymerisation rate on initiating adduct concentration. In the expected kinetic scheme the polymerisation rate V_p would have been proportional to the concentration of both the active species $[P^*]$ and monomer [M] [Equation 8].

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[49] Muller, A.H.E., Zhuang, R., Yan, D., Ltvinenko, G., Macromolecules, **1995**, 28, 4326-4333

[50] Veregin, R.P.N., Odell, P.G., Michalak, L.M., Georges, M.K., Macromolecules, **1996**, 29, 3346-3352

[51] Catala, J.M., Bubel, F., Oulad Hammouch, S., Macromolecules, **1995**, 28, 8441-8443

$$V_p = -\frac{d[M]}{dt} = k_p[M][P^*]$$

Equation 8

From the equilibrium between the dormant and growing chains [Figure 61]

$$P{-}T \underset{}{\overset{K}{\rightleftharpoons}} P^{\bullet} + T^{\bullet}$$

Figure 61

We might expect an equation describing the rate of polymerisation [Equation 9]

$$V_p = k_p[M]K^{\frac{1}{2}}[P-T]^{\frac{1}{2}}$$

Equation 9

and the concentration of propagating radicals to be [Equation 10]

$$[P^{\bullet}] = k^{\frac{1}{2}}[P-T]^{\frac{1}{2}}$$

Equation 10

From the capping/homolysis equilibrium we might expect [Equation 11]

$$K = \frac{[P^{\bullet}][T^{\bullet}]}{[P-T]} = [P^{\bullet}]^2[P-T]$$

Equation 11

Since the equilibrium between homolysis and capping reactions is likely to lie mainly towards the capped chain ends the concentration of [P-T] was assumed to be approximately equal to the initiating adduct concentration [I] resulting in [Equation 12]

$$V_p = k_p[M]K^{\frac{1}{2}}[I]^{\frac{1}{2}}$$

Equation 12

or using a logarithmic conversion index [Equation 13]

$$\ln([M_0]/[M]) = k_p K^{\frac{1}{2}} [I]^{\frac{1}{2}} t$$

Equation 13

Assuming each initiating molecule results in one propagating polymer chain this kinetic scheme results in a linear plot of logarithmic conversion index with time, the slope of which is proportional to the square root of the initiator concentration. Greszta and Matyjaszewski[52] commenting on this work noted the similarity in the rate of nitroxide mediated polymerisation with that of thermal autopolymeriation and suggested that this might be the determining factor in polymerisation rate.

Fukuda and Terauchi[53] compared the rates of nitroxide mediated polymerisation with either di-*tert*-butyl nitroxide or TEMPO with thermal autopolymerisations finding good agreement in each case. The results of quantitative ESR studies and dilatometry were used to calculate values for polymerisation rate constants. For a given adduct molecule this resulted in the estimation that dissociation occurs on average once every one hundred seconds with 0.3 styrene units adding before recombination 2×10^{-5}s after dissociation. Both a sufficiently high value for dissociation/capping equilibrium constant of the P-N adduct resulting in frequent dissociation and the feed of new radicals into the polymerisation were suggested to be essential for a successful polymerisation. The TEMPO mediated polymerisation of styrene was shown to meet these kinetic requirements.

Examination by Fukuda *et al.*[54] of the kinetic scheme in polymerisation of styrene in the presence of unimolecular TEMPO based initiator resulted in differential

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[52] Gretszta, D., Matyjaszewski, K., Macromolecules, **1996**, 29, 5239-5240

[53] Fukuda, T., Terauchi, T., Chemistry Letters, **1996**, 293-294

[54] Fukuda, T., Terauchi, T., Goto, A., Ohno, K., Tsujii, Y., Miyamoto, T., Kobatake, S., Yamada, B., Macromolecules, **1996**, 29, 6393-6398

equations describing the time dependent concentrations of propagating and mediating radicals.

$$\frac{d[P^*]}{dt} = R_i - k_t[P^*]^2 + k_d[P-N] - k_c[P^*][N^*]$$

Equation 14

$$\frac{d[N^*]}{dt} = k_d[P-N] - k_c[P^*][N^*]$$

Equation 15

where R_i is the rate of initiation due to added initiator or thermal autoinitiation and k_t is the rate constant for termination.

In a polymerisations in which only an initiating alkoxyamine adduct and monomer are present, when raised to elevated temperature the alkoxyamine will begin to dissociate to form propagating and mediating radicals. The concentrations of these radicals will rise rapidly to a concentration determined by the equilibrium between the homolysis and capping reactions. In the absence of further initiation transient radicals will be continually removed by termination. The resulting build up in excess of mediating nitroxide would result in the cessation of polymerisation as this shifts the capping/homolysis equilibria towards the capped chain ends. Initiation, whether through added initiator or thermal autopolymerisation, however, produces fresh radicals which prevent the build up of an excess of mediating nitroxide and a steady state is reached. Assuming steady state conditions the rate of change in concentration of propagating and capping species can be set to zero [Equation 16], this scheme results in equations for the transient propagating [Equation 17] and mediating [Equation 18] radicals.

$$\frac{d[P^*]}{dt} = \frac{d[N^*]}{dt} = 0$$

Equation 16

$$[P^*] = (R_i / k_t)^{\frac{1}{2}}$$

Equation 17

$$[N^*] = K[P - N] / [P^*]$$

Equation 18

The resulting steady rate of polymerisation can be described in a number of ways [Equations 19-21]

$$R_p = -\frac{d[M]}{dt}$$

Equation 19

$$R_p = k_p [P^*][M]$$

Equation 20

$$R_p = (k_p{}^2 R_i / k_t)^{\frac{1}{2}} [M]$$

Equation 21

The resulting equation for polymerisation rate is independent of the initiating adduct concentration and identical to that obtained for autopolymerisation in the absence of initiator and mediating nitroxide mediating nitroxide.

Matyjaszewski[55] computationally modelled the differential equations for TEMPO mediated radical polymerisation taking into account autoinitiation, termination, transfer and chain end decomposition reactions. These simulations successfully

[55] Gretszta, D., Matyjaszewski, K., Macromolecules, **1996**, 29, 7661-7670

emulated the features of real nitroxide mediated systems in terms of rate, molecular weight evolution, polydispersity and reactant concentration profiles. Yang *et al.*[56] applied a Monte Carlo computational method to simulate the kinetics of nitroxide mediated polymerisations including initiation, propagation, chain termination, thermal initiation, and chain end decomposition reactions. This successfully predicted the essential features of living free radical polymerisation with stepwise growth of molecular weight with time, low polydispersity, and the appearance of the persistent radical effect.

A kinetic analysis of living radical polymerisation was presented by Fischer[57] taking into account the persistent radical effect. The "persistent radical effect" is a term coined by Finke for the general mechanism proposed by Fischer describing the specific crosscoupling observed between two radicals formed at equal rates when one species is persistent and the other transient. This selectivity was explained because of initial self termination of the transient radical which results in a build up of an excess in the persistent radical. Since its first observation, this selectivity in cross coupling has seen significant application in synthetic chemistry[58]. Analysis was carried out by Fischer into the kinetics of free radical polymerisation for systems initiated by a stoichiometric, or unimolecular, initiator and equations derived predicting polymerisation features in agreement with those which are obtained experimentally, namely a linear increase of molecular weight with conversion, low polydispersity and a decrease in polydispersity with conversion which then reverses at high conversion.

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[56] He, J., Zhang, H., Chen, J., Yang, Y., Macromolecules, **1997**, 30, 8010-8018

[57] Fischer, H., Macromolecules, **1997**, 30, 5666-5672

[58] Studer, A., Chem. Eur. J., **2001**, 7, 6, 1159

This examination of the reaction kinetics was later extended[59] in order to examine whether the reversible capping of propagating polymer chains is a true equilibrium and under which kinetic conditions this equilibrium is maintained.

Starting with initiator and zero radical concentration at time zero radicals are formed at a rate governed by k_d. Once the radical concentration reaches a significant level the termination and combination reactions become significant and as transient radicals are removed by termination an excess of persistent radicals results.

This examination resulted in equations describing the concentrations of propagating [Equation 22] and mediating radicals [Equation 23]

$$[R] = \left(\frac{K[I]_0}{3k_t} \right)^{\frac{1}{3}} t^{-\frac{1}{3}}$$

Equation 22

$$[N^*] = \left(3k_t K^2 [I]_0^{\,2}\right)^{\frac{1}{3}} t^{\frac{1}{3}}$$

Equation 23

from these equations we obtain an expression [Equation 24]

$$k_c [R][N^*] = k_d [I]_0$$

Equation 24

confirming the equilibrium between capped and uncapped chain ends. This holds for the conditions [Equation 25]

$$\frac{k_d}{k_c} = K < [I]_0 k_c / 4k_t$$

Equation 25

[59] Fischer, H., Journal of Polymer Science: A: Polymer chemistry, **1999**, 37, 1885-1901

During the period in which equilibrium conditions apply the concentration of dormant polymer is largely equivalent to the initiating adduct concentration [I] resulting in the expression describing the rate of polymerisation [Equation 26].

$$[M]/[M_0] = \exp\left(\frac{-3}{2} k_p \left(\frac{K[I]_0}{3k_t}\right)^{\frac{1}{3}} t^{\frac{2}{3}}\right)$$

Equation 26

Application of these equations in simulation of polymerisation led to predictions for persistent radical concentration, polymerisation rate and polydispersity index consistent with those values experimentally obtained. The dependence of polymerisation rate on thermal autopolymerisation was shown to be dependent on the rate constants of the polymerising system. Those polymerisations with rate constants within the described conditions operating under a kinetic regime in which a dependence on initiating adduct concentration should be observed.

The influence of the persistent radical effect on equilibrium between free nitroxide and propagating chain ends was studied[60] using quantitative ESR, in which a steep initial increase in nitroxide concentration was observed with a slower subsequent increase over the timescale of the polymerisation in agreement with the predictions of Fischer.

The ability of certain monomer and nitroxide combinations to undergo polymerisation in the absence of a further source of radicals was demonstrated by Fukuda *et al.*[61] who studied the polymerisation of a functionalised styryl

[60] MacLeod, P.J., Veregin, R.P.N., Odell, P.G., Georges, M.K., Macromolecules, **1998**, 31, 530-531

[61] Ohno, K., Tsujii, Y., Miyamoto, T., Fukuda, T., Goto, M., Kobayashi, K., Akaike, T., Macromolecules, **1998**, 31, 1064-1069

glycomonomer in which autoinitiation was described as being absent to any significant degree. Attempts to mediate polymerisation utilising TEMPO mediating nitroxide showed no significant conversion while the use of di-*tert*-butyl nitroxide, with which equilibrium is likely to lie more towards the dissociated radical species, was successful in producing polymer with both a linear increase in molecular weight and low product polydispersity. The rate of polymerisation and final conversion were both shown to be dependent on the initiating adduct concentration.

Fischer *et al.*[62] verified the influence of the persistent radical effect in alkoxyamine homolysis through investigation of nitroxide formation from homolysis of 2-phenyl-2-(2',2',6',6'-tetramethylpiperidine-1'-oxyl)propane, cumyl TEMPO, [Figure 62] in the absence of a radical scavenger with which the expected $t^{1/3}$ time dependence of TEMPO concentration was observed.

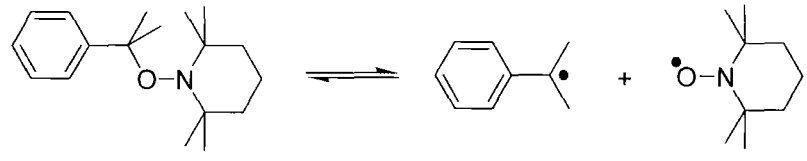

Figure 62 Homolysis of 2-phenyl-2-(2',2',6',6'-tetramethylpiperidine-1'-oxyl)propane

Further analysis by Fischer and Souaille[63] of the kinetic conditions for living and controlled free radical polymerisation presented analytical equations describing the concentrations of radical, monomer, dormant and dead polymer chains, molecular weight and polydispersity.

For those polymerisations in which the rate constants for homolysis, capping and propagation are close to but not within the conditions for polymerisation determined

[62] Kothe, T., Marque, S., Martschke, R., Popov, M., Fischer, H., J., Chem. Soc., Perkin Trans. 2, **1998**, 1553-1559

[63] Souaille, M., Fischer, H., Macromolecules, **2000**, 33, 7378-7394

by the persistent radical effect it was shown that either a living polymer with poor control or a non-living polymer with low polydispersity may be obtained.

Rate Acceleration in Nitroxide Mediated CRP

Initial thought that autoinitiation in styrene might result in an increased polydispersity led to a study[64] describing efforts to improve macromolecular control by limiting autoinitiation. Nitroxide controlled radical polymerisation of styrene was carried out utilising a bimolecular system of TEMPO nitroxide with benzoyl peroxide with the addition of camphor sulfonic acid. A prior study[65] had shown camphor sulfonic acid to reduce the autopolymerisation rate of styrene. This resulted in a significantly enhanced rate of polymerisation although this increase in rate was attained at the expense of some polydispersity control.

Studies[66] carried out using ESR spectroscopy to investigate the mechanism of camphor sulfonic acid rate acceleration suggested that this rate enhancement is due to the removal of TEMPO from the reaction. Other polar additives were also examined as potential accelerating species, the most effective of these was shown to be 2-fluoro-1-methyl-pyridinium-*p*-toluenesulfonate which was demonstrated to enhance polymerisation rate without measurable consumption of the mediating species.

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[64] Georges, M.K., Veregin, R.P.N., Kazmaier, P.M., Hamer, G.K., Saban, M., Macromolecules, **1994**, 27, 7228-7229

[65] Buzanowski, W.C., Graham, J. D., Priddy, D.B., Shero, E., Polymer, **1992**, 33, 14, 3055

[66] Odell, P.G., Veregin, R.P.N., Michalak, L.M., Brousmiche, D., Georges, M.K., Macromolecules, **1995**, 28, 8453-8455

The mechanism of additive acceleration of polymerisation rate by camphor sulfonic acid was examined[67] by measurement of the free nitroxide concentration. This concentration was shown to be reduced ten fold by the addition of camphorsulfonic acid. The increase in polymerisation rate and product polydispersity was ascribed to the reduction in capping radical concentration. The accelerated polymerisation rate observed with other polar additives was suggested to be due to some polarity influence on the rate of homolysis and capping reactions.

The mechanism of polymerisation rate acceleration with polar additives was further studied by Scaiano *et al.*[68] who measured the rate of transient radical trapping by nitroxide in the presence of organic acids. This resulted in the observation of a significant reduction in radical trapping rate although this was thought to be too small to solely account for the increased polymerisation rate. It was also suggested that additives may similarly influence the rate of alkoxyamine homolysis.

The accelerating effect of a further series of additives was assessed by Hawker *et al.*[69]. The addition of acylating agents resulted in improved rates of polymerisation without any significant increase in polydispersity.

The mechanism of this acceleration through use of acylating agents was examined by Fukuda *et al.*[70] using a GPC resolution method to study the activation rate of an alkoxyamine terminated polymer species. No change in activation rate was observed on acylation agent addition although the potential acylation of free nitroxide to reduce capping efficiency was not ruled out.

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[67] Veregin, R.P.N., Odell, P.G., Michalak, L.M., Georges, M.K., Macromolecules, **1996**, 29, 4161-4163

[68] Baldovi, M.V., Mohtat, N., Scaiano, J.C., Macromolecules, **1996**, 29, 5497-5499

[69] Malmström, E., Miller, R.D., Hawker, C.J., Tetrahedron, **1997**, 53, 15225-15236

[70] Goto, A., Tsujii, Y., Fukuda, T., Chemistry Letters, **2000**, 768-789

Fukuda *et al.*[71] investigated the kinetic consequences of the addition of an initiator with a long lifetime to the polymerising system. The addition of initiator was observed to result in a three-fold increase in the rate of polymerisation without significant increase in product polymer polydispersity. The slow addition of initiators with shorter lifetimes has also been used by Yang *et al.*[72] to achieve substantially the same effect. The effect of rate enhancement by several mechanisms have since been incorporated by Yang *et al.*[73] into calculations of kinetics and molecular weight distributions by Monte Carlo algorithms developed previously.

Nitroxide Development

Since the early work utilising the TEMPO nitroxide in mediation of controlled radical polymerisation a number of novel nitroxides have been applied to controlled radical polymerisation, which from studies into the alkoxyamine homolysis and nitroxide capping reactions might be expected to have significantly different equilibrium constants between capping and homolysis reactions.

Sogah and Puts[74] demonstrated the use of a 2,5-dimethyl-2,5-diphenyl pyrrolidine-N-oxyl nitroxide in conjunction with benzoyl peroxide [Figure 63] to mediate polymerisation of styrene at a rate approximately two times faster than that reported for a comparable TEMPO mediated system.

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[71] Goto, A., Fukuda, T., Macromolecules, **1997**, 30, 4272-4277

[72] He, J., Chen, J., Li, L., Pan, J., Li, C., Cao, J., Tao, Y., Hua, F., Yang, Y., McKee, G.E., Brinkmann, S., Polymer, **2000**, 41, 4573-4577

[73] He, J., Li, L., Yang, Y., Macromol. Theory. Simul., **2000**, 9, 463-468

[74] Puts, R.D., Sogah, D.Y., Macromolecules, **1996**, 29, 3323-3325

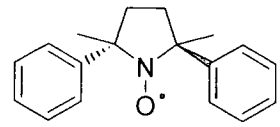

Figure 63 2,5-dimethyl-2,5-diphenyl pyrrolidine-N-oxide nitroxide

1,1,3,3-tetraethylisoindilone-2-oxyl, TEISO nitroxide [Figure 64] was used by Busfield *et al.*[75] to prepare a unimolecular alkoxyamine initiator for the low temperature polymerisation of styrene although this study met with limited success. Although this nitroxide has increased steric bulk the polymerisation efficiency may have been reduced as a result of poor choice of initiating radical segment.

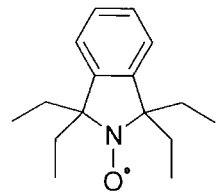

Figure 64 1,1,3,3-tetraethylisoindilone-2-oxyl nitroxide

Several derivatives of 2,2',5,5'-tetraalkylimidazolidin-4-one-1-oxyls have been used by Moad *et al.*[76] as potential mediating species for styrene and methacrylate polymerisations with improved rate observed in comparison with TEMPO mediated systems.

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[75] Cresidio, S.P., Aldabbagh, F., Busfield, W.K., Jenkins, I.D., Thang, S.H., Zayas-Holdsworth, C., Zetterlund, P.B., Journal of Polymer Science Part A: Polymer Chemistry, **2001**, 39, 1232-1241

[76] Chong, Y.K., Ercole, F., Moad, G., Rizzardo, E., Thang, S.H., Macromolecules, **1999**, 32, 21, 6895-6903

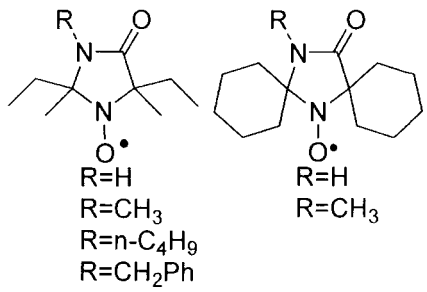

Figure 65 2,2,5,5 tetraalkylimidazolidin-4-one-1-oxyl derivatives

Di-*tert*-butyl nitroxide [Figure 66] has been studied in polymerisation of styrene and in the polymerisation butyl acrylate. This was achieved through addition of a small amount of additional initator although a significant level of chain end decomposition was observed.

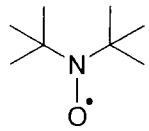

Figure 66 di-*tert*-butyl nitroxide

Recent work in novel nitroxides for controlled radical polymerisation has centred on the use of nitroxides with a hydrogen substituent adjacent to the nitroxide functionality.

It was long held[77] that nitroxides with hydrogen substituents adjacent to nitroxide are unstable through a disproportionation reaction although this is dependent on both steric requirement for close encounter and intrinsic hydrogen reactivity.

Benoit *et al.*[78] identified the N-*tert*-butyl-N-[1-diethylphosphono(2,2-dimethylpropyl)]nitroxide, DEPN [Figure 67] through screening of polymerisation characteristics of a variety of nitroxides obtained through the oxidation of α-N-

[77] Advances in Free Radical Chemistry, Vol 1., **1990**, JAI Press Inc., 253-295

[78] Grimaldi, S., Finet, J.P., Le Moigne, F., Zeghdaoui, A., Tordo, P., Benoit, D., Fontanille, M., Gnanou, Y., Macromolecules, **2000**, 33, 1141-1147

alkylamino phosphonic acid esters. Use of this nitroxide as mediating species in bimolecular initiation of styrene polymerisation with AIBN resulted in an improved rate over comparable TEMPO mediation. This nitroxide was also shown to be capable of mediating butyl acrylate polymerisation.

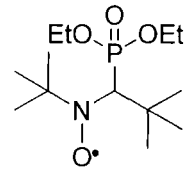

Figure 67 N-tert butyl-N-[1-diethylphosphono(2,2-dimethylpropyl)]nitroxide, DEPN

The kinetics and mechanism of the polymerisation of styrene and butyl acrylate utilising DEPN have been studied[79] confirming the observation of a significantly increased polymerisation rate in styrene over that observed with other nitroxide systems whilst maintaining macromolecular control.

Examination of the polymerisation kinetics allowed calculation of dissociation rate constants over a temperature range and hence the construction of an Arrhenius plot. This plot was used to calculate the activation energy for the homolysis dissociation of the capped chain end as being 121 $kJmol^{-1}$. This activation energy is approximately the same as that previously calculated for TEMPO based alkoxyamines. The increased dissociation rate constant was suggested to be a consequence of a larger Arrhenius frequency pre-factor, generally related to the reaction entropy, resulting from steric hinderance in the open chain nitroxide in comparison to the six membered ring.

[79] Benoit, D., Grimaldi, S., Robin, S., Finet, J.P., Tordo, P., Gnanou, Y., J. Am. Chem. Soc., **2000**, 122, 5929-5939

The kinetics of DEPN mediated polymerisation of styrene were again studied[80] through examination of variation in the rate of polymerisation with temperature. Construction of an Arrhenius plot resulted in calculation of homolysis equilibria constant of $k=1.45x10^7exp(-113.5kJmol^{-1}/RT)$. Comparison of this equilibria constant with the equivalent TEMPO polymerisation suggests that the equilibria between capped and free species with DEPN is markedly shifted towards the active species. Similar study[81] into the kinetics of butyl acrylate polymerisation resulted in a calculated value for the equilibrium constant of $k=4.93x10^5exp(-119.3kJmol^{-1}/RT)$. This study also proposed the introduction of an excess of nitroxide to retard the polymerisation rate of acrylate species which would otherwise progress very rapidly. The kinetics of DEPN polymerisation were shown[82] to be in agreement with those features predicted from the kinetic scheme determined by the persistent radical effect rather than that determined by the rate of autoinitiation e.g. 2/3 order rate dependence on time and 1/3 order rate dependence in initiating alkoxyamine concentration.

Hawker *et al.*[83] screened a variety of nitroxides in controlled radical polymerisation as their styryl alkoxyamine adducts. These nitroxides were utilised in the polymerisation of styrene and *n*-butyl acrylate in order to assess their potential as mediating species. The open chain nitroxides [Figure 68] were observed to be the most effective in the polymerisation of styrene. The utility of these nitroxides in

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[80] Lacroix-Desmazes, P., Macromol. Chem. Phys., **2000**, 201, 662-669

[81] Lacroix-Desmazes, Lutz, J.F., Chauvin, F., Severac, R., Boutevin, B., Macromolecules, **2001**, 34, 8866-8871

[82] Lutz, J.F., Lacroix-Desmazes, P., Boutevin, B., Macromol. Rapid. Commn., **2001**, 22, 189-193

[83] Benoit, D., Chaplinski, V., Braslau, R., Hawker, C.J., J. Am. Chem. Soc., **1999**, 121, 3904-3920

mediation of acrylates, acrylamide and acrylonitrile monomers and in the synthesis of random and block copolymers was also demonstrated.

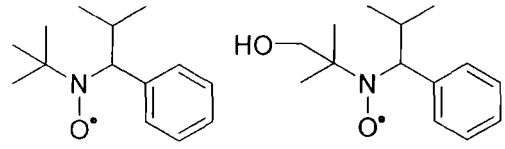

Figure 68 Open chain nitroxides from Hawker's screening

The chain end fidelity of the nitroxides identified by Hawker *et al.* was examined[84] through the use of alkoxyamines with chromophores tethered to either nitroxide or initiating segments. This suggested that incorporation of the end groups into polymer is high up to large molecular weight allowing the reliable synthesis of telechelic and block copolymers. This is in contrast with TEMPO mediated polymerisation in which the chain end group fidelity was shown to become poor at relatively low molecular weight.

Variations on these structures have since developed by Hawker *et al.*[85] with the additional hydroxy groups [Figure 69], which have been shown to further improve the polymerisation rate.

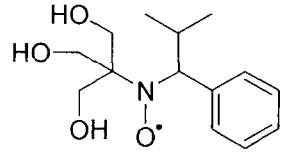

Figure 69 Hydrogen bonding group open chain nitrogen

This is in accordance with work by Studer *et al.* which reported an increased in dissociation rate constants for hydroxy-substituted alkoxyamine capable of intramolecular hydrogen bonding. In order to investigate whether this acceleration is

[84] Rodlert, M., Harth, E., Rees, I., Hawker, C.J., Journal of Polymer Science A Polymer Chemistry, **2000**, 38, 4749-4763

[85] Harth, E., Van Horne, B., Hawker, C.J., Chem. Comm., **2001**, 823-824

a direct result of the addition of hydroxyl groups to the nitroxide the protected analogue was prepared in which the hydroxy groups are tethered [Figure 70]. This alkoxyamine proved to be a poor initiator for the monomers studied.

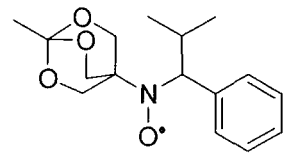

Figure 70 Protected alkoxyamine

Recent work by Catala[86] has shown that the nitroxides N-*tert*-butyl-N (1-tertbutyl-2-ethyl sulfinyl) propyl nitroxide and its structural analogue N-*tert*-butyl-N-(1-*tert*-butyl-2-methyl) pentyl nitroxide [Figure 71] are promising potential mediating species for the low temperature polymerisation of styrene although polymerisation takes place over a long time period.

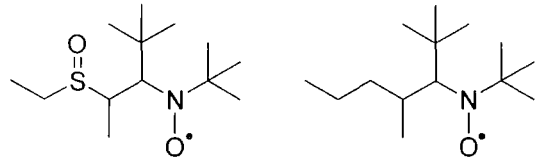

Figure 71 N-*tert*-butyl-N (1-*tert*-butyl-2-ethyl sulfinyl) propyl nitroxide and N-*tert*-butyl-N-(1-*tert*-butyl-2-methyl) pentyl nitroxide

Alkoxyamine Synthesis

The initial demonstration by Hawker *et al.* unimolecular initiation utilised an alkoxyamine prepared through the reaction of benzoyl peroxide with styrene in the presence of TEMPO nitroxide.

[86] Drockenmuller, E., Catala, J-M,. Macromolecules, **2002**, 35, 2461-2466

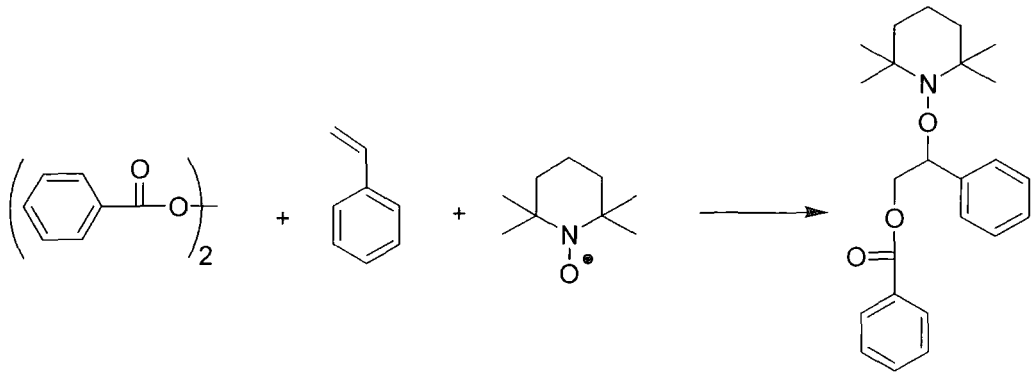

Figure 72 Alkoxyamine synthesis through reaction of benzoyl peroxide with styrene

Subsequent to this, a number of groups have investigated synthetic routes to prepare unimolecular initiators.

Photochemical routes to the formation of alkoxyamines were demonstrated by Scaiano *et al.*[87] through the trapping by nitroxide of a benzylic radical formed via hydrogen abstraction by a photoinitiator from benzylic alkane [Figure 73] achieving yields of between 90 and 95 %.

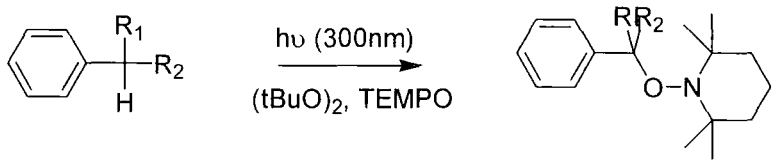

Figure 73 Photogenerated radical abstraction of benzylic hydrogen route to alkoxyamines

The trapping by nitroxides of radicals resulting from photolysis of brominated species was also demonstrated [Figure 74].

[87] Connolly, T.J., Baldovi, N.M., Mohtat, N., Scaiano, J.C., Tetrahedron Letters, **1996**, 37, 28, 4919-4922

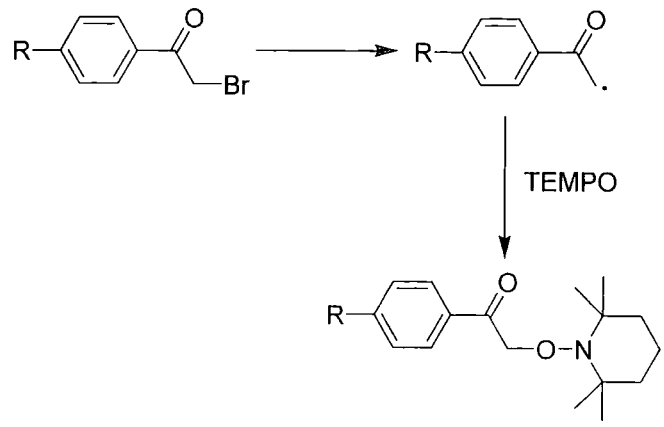

Figure 74 Photogenerated radical from bromo alkane route to alkoxyamine

This was also applied to difunctional bromo species to form difunctional alkoxyamine species although the yields obtained were variable.

In a similar fashion to the photochemical approach taken by Scaiano the abstraction of hydrogen from benzylic species was used by Miura *et al.*[88-89] using a di-*tert*-butyl peroxalate initiator to generate benzylic radicals at low temperature in the presence of stable nitroxides to prepare alkoxyamines [Figure 75].

[88] Miura, Y., Hirota, K., Moto, H., Yamada, B., Macromolecules, **1998**, 31, 4659-4661

[89] Miura, Y., Hirota, K., Moto, H., Yamada, B., Macromolecules, **1999**, 32, 8356-8362

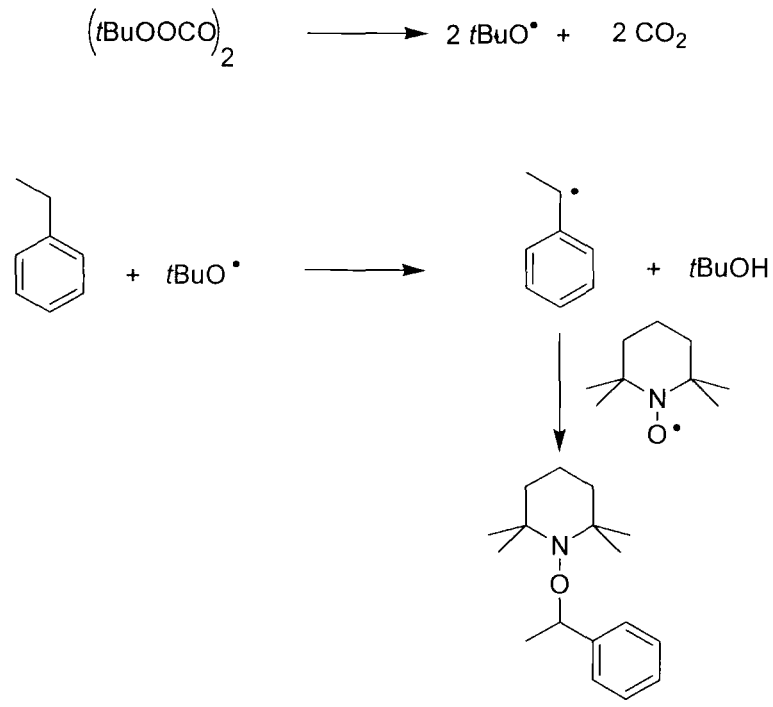

Figure 75 Low temperature initiator radical abstraction of benzylic hydrogen route to alkoxyamine

A number of low temperature routes to the synthesis of alkoxyamines were demonstrated by Braslau *et al.*[90] through generation of transient carbon centred radicals with mild oxidising reagents which do not oxidise nitroxide species.

An in-situ formed hydrazine from a brominated species was oxidised with lead oxide resulting in the formation of a carbon centred radical which is subsequently trapped with a nitroxide to form an alkoxyamine in ~78% yield [Figure 76].

[90] Braslau, R., Burrill, L.C., Siano, M., Naik, N., Howden, R.K., Mahal, L.K., Macromolecules, **1997**, 30, 6445-6450

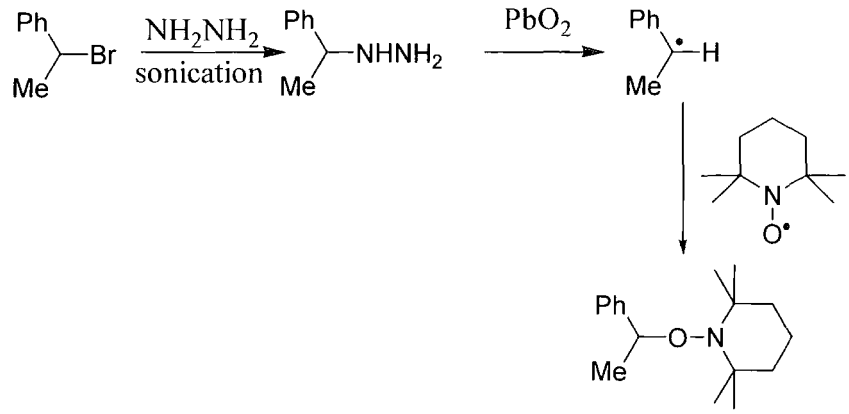

Figure 76 Hydrazine oxidation route to alkoxyamine

Radical formation through oxidation of a lithium enolate by copper II chloride in the presence of a nitroxide resulted in the formation of an alkoxyamine in ~50% yield [Figure 77].

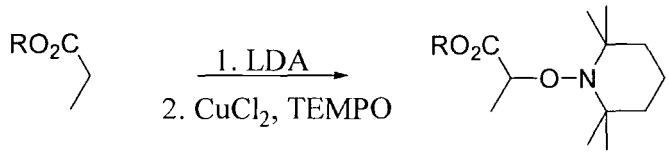

Figure 77 Oxidation of lithium enolate route to alkoxyamine

Alkoxyamine synthesis was also demonstrated from radical trapping in the presence of nitroxide from photolysis of a cyclopentadienyl iron dicarbonyl dimer, Fp dimer resulting in a yield of 65% [Figure 78].

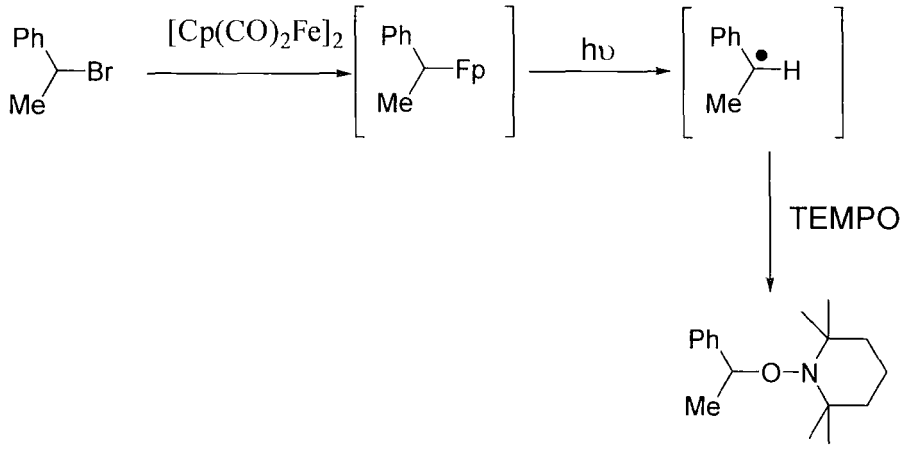

Figure 78 Cyclopentadienyl iron dicarbonyl photochemical route to alkoxyamine

A photochemically initiated diphenyl disulfide initiator was used to attack a vinyl unsaturated species with trapping of the carbon centred addition radical, albeit in a poor yield of 9% [Figure 79].

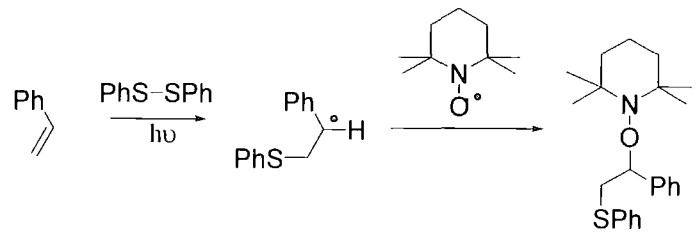

Figure 79 diphenyl disulfide photochemical route to alkoxyamine

A route to alkoxyamines was also demonstrated through the abstraction of hydrogen from solvent in diethyl ether or THF by *tert*-butoxy radicals to form radicals subsequently trapped by nitroxides although reaction times were long and yields low [Figure 80].

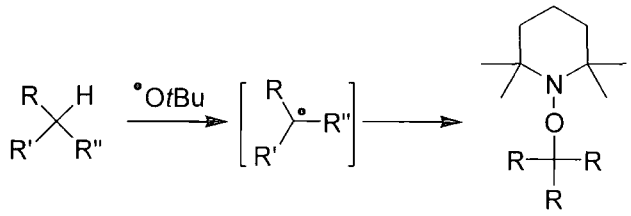

Figure 80 Photogenerated radical abstraction from diethyl ether or THF hydrogen route to alkoxyamine

Matyjaszewski *et al.*[91] demonstrated the synthesis alkoxyamines via trapping by nitroxide of radical generated from from alkyl halides via catalysis based on the ATRP process [Figure 81]. The product alkoxyamines were isolated in yields of 70-95% from the reaction media simply by passing through alumina to remove excess catalyst and nitroxide.

[91] Matyjaszewski, K., Woodworth, B.E., Zhang, X., Gaynor, S.G., Metzner, Z., Macromolecules, **1998**, 31, 5955-5957

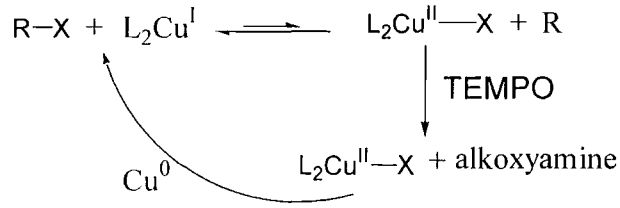

Figure 81 ATRP catalysis route to alkoxyamine formation

Meisenheimer rearrangements of tertiary amine odixes were proposed by Bergbreiter and Walchuck[92] as a potential route for the preparation of alkoxyamine initiators [Figure 82]. TEMPO based alkoxyamines were prepared from N-allyl substituted 2,2,6,6-tetramethyl piperidine.

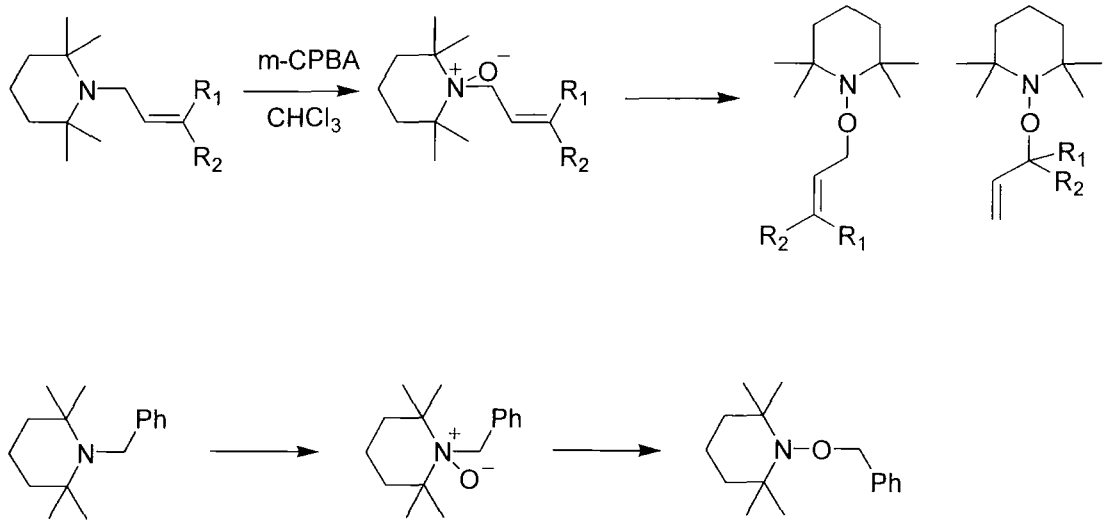

Figure 82 Meisenheimer rearrangements to alkoxyamines

Wu and Wang[93] proposed the trapping by nitroxide of radicals directly formed from initiators to prepared alkoxyamines claiming [Figure 83].

[92] Bergbreiter, D.E., Walchuck, B., Macromolecules, **1998**, 31, 6380-6382

[93] Wang, D., Wu, Z., Macromolecules, **1998**, 31, 6727-6729

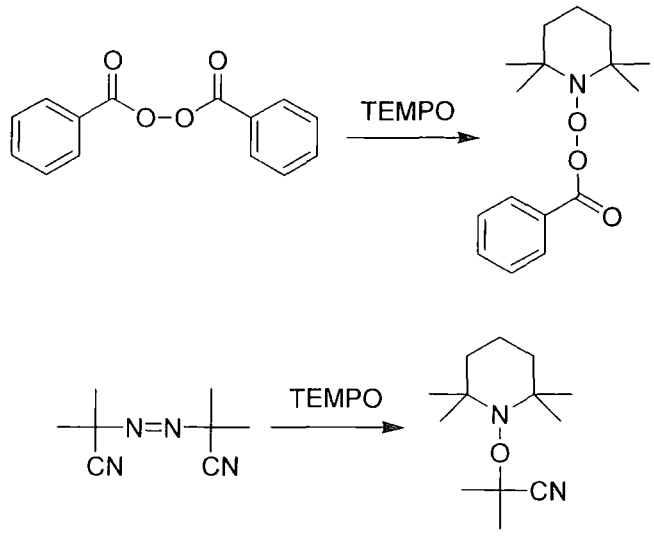

Figure 83 Direct reaction of initiator with nitroxide route to alkoxyamines

A catalytic route utilising Jacobsen's catalyst, a manganese species more conventionally used in the generation of chiral epoxides, was developed by Hawker *et al.*[94] to prepare alkoxyamines from nitroxide in high yield [Figure 84].

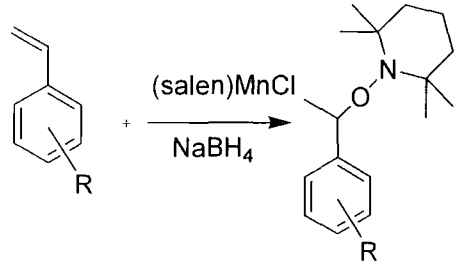

Figure 84 Jacobsen's catalyst route to alkoxyamines

This catalytic approach was used in the preparation of several para-substituted alkoxyamines in yields between 57-70%. This approach was also used with 4-vinyl styrene to prepared bifunctional initiators.

Novel Macromolecular Architectures

Controlled radical polymerisations offer the prospect of robust synthetic routes to a wide variety of novel macromolecular architectures. These include controlled

[94] Dao, J., Benoit, D., Hawker, C.J., Journal of Polymer Science: Part A: Polymer Chemistry, 36, 2161-2167

molecular weights, block copolymers, controlled molecular weight distributed copolymers, end functionalised, telechelic, controlled weight side chain, star-like, highly branched and well defined macromolecular networks [Figure 85].

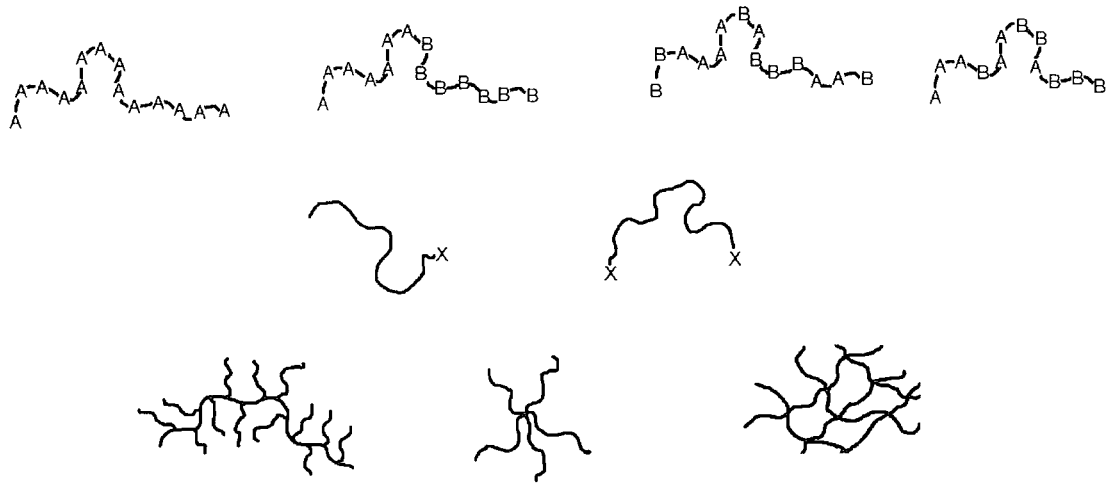

Figure 85 Potential macromolecular architectures

Examples from the original patent covering the use of nitroxides in controlled radical polymerisation have shown the synthesis of low polydispersity (typically less than 1.1), homopolymers of targeted molecular weight. The formation of an alkoxyamine species at one terminus is a natural consequence of the polymerisation mechanism and has been used for functionalisation to generate end functional polymer.

The living nature of the polymerisation allows the formation of block copolymers via a number of potential processes

- Controlled radical polymerisation with sequential addition of one monomer followed by another
- Funtionalisation of a presynthesised polymer to generate alkoxyamine terminus end groups followed by controlled polymerisation
- Difunctional initiator allowing polymerising by combination of controlled radical polymerisation with another polymerisation technique

- The capping of a radical polymerising system by addition of nitroxide to form an alkoxyamine macroinitiator

The new generation of α-hydrogen nitroxides have greatly increased the variety of monomer species which can be incorporated into polymer.

A number of groups have synthesised block copolymers by the sequential addition of monomers to form macroinitiators which are then used to initiate the polymerisation of dissimilar monomer[95-100]. This sequential method has interestingly been used to prepare unusual polymer structures such as a diblock copolymer with coil and liquid crystal blocks[101&102]. The synthesis of controlled morphology amphiphilic copolymers, which are difficult to achieve by other methods, such as poly(styrene-b-sodium styrene sulfonate)[103], poly (N-hexadecyl-4-vinyl pyridinium bromide –b-N,N-dimethyl acrylamide)[104], and poly(sodium styrene sulphonate-b-vinyl

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[95] Lokaj, J., Vlček, P., Kříž, J., Macromolecules, **1997**, 30, 7644-7646

[96] Listigovers, Macromolecules, **1996**, 29, 8992-8993

[97] Benoit, D., Hawker, C.J., Huang, E.E., Lin, Z., Russell, T.P., Macromolecules, **2000**, 33, 1505-1507

[98] Jousseet,., Oulad Hammouch, S., Catala, J-M., Macromol., **1997**, 30, 6685-6687

[99] Benoit, D., Harth, E., Fox, P., Waymouth, R., M., Hawker, C.J., Macromol., **2000**, 33, 363-370

[100] Yousi, Z., Jian, L., Rongchuan, Z., Jianliang, Y., Lizong, D., Lansun, Z., Macromol., **2000**, 33, 13, 4745-4749

[101] Bignozzi, M.C., Ober, C.K., Laus, M., Macromolecular Rapid Commmun, **1999,** 20, 622-627

[102] Wan, X., Tu, Y., Zhang, D., Zhou, Q., Polymer International, **2000**, 49, 243-247

[103] Bouix, M., Gouzi, J., Charleux, B., Vairon, J-P., Guinot, P., Macromolecular Rapid Communications, **1998**, 19, 209-213

[104] Fischer, A., Brembilla, A., Lochon, P., Polymer, **2001**, 42, 1441-1448

naphthalene)[105] and poly(styrene sodium sulfonate-b-N-vinyl carbazole)[106] has also been shown.

The functionalisation to alkoxyamine of polystyrene prepared by anionic polymerisation to an alkoxyamine terminated polymer has been demonstrated[107]. This approach has also been used with the anionic polymerisation of butadiene to form alkoxyamine which was then used as a macroinitiator for the polymerisation of styrene to form block copolymer[108] and been used to synthesise interesting block copolymers from conjugated macroinitiator with a view to further use as photonic materials[109].

Block copolymers can also be prepared by the complement of nitroxide mediated polymerisation with another polymerisation technique such as ring opening polymerisation[110] or thermally initiated complementary radical polymerisation[111]

Significantly, the use of a free radical polymerisation allows the preparation of tailored distributed copolymers. Anionic and cationic polymerisations are highly selective between monomers whereas the reduced selectivity of radicals allows the incorporation of different comonomers into the backbone depending on the reactivity

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[105] Nowakowska, M., Zapotoczny, S., Karewicz, A., Macromolecules, **2000**, 33, 7345-7348

[106] Charleux, B., Macromolecular Rapid Communications, **1998**, 19, 209-213

[107] Yoshida, E., Ishizone, T., Hirao, A., Nakahama, S., Takata, T., Endo, T., Macromolecules, **1994**, 27, 12, 3119-3124

[108] Kobatake, S., Harwood, H.J., Quirk, R.P., Priddy, D.B., Macromolecules, **1998**, 31, 3735-3739

[109] Stalmach, U., de Boer, B., Post, A.D., van Hutten, P.F., Hadziioannou, G., Angew. Chem. Int. Ed. **2001**, 40, 2, 428-430

[110] Hawker, C.J., Hedrick, J.L., Malmström, E.E., Trollsås, M., Mecerreyes, D., Moineau, G., Dubois, Ph., Jérôme, R., Macromolecules, **1998**, 31, 2, 213-219

[111] Gravert, D.J., Janda, K.D., Tetrahedron Letters, **1998**, 39, 1513-1516

ratio values. Nitroxide mediated polymerisation reaction has been used to prepare well defined distributed random[112] and alternating[113] copolymers.

It was suggested that well defined block, random and segmented arborescent polymers might be prepared via copolymerisation through nitroxide mediated polymerisation of styrene and chloromethyl styrene followed by functionalisation of the chloromethyl sites with an organolithium species [114&115]. This was demonstrated for the synthesis of a variety of brush architectures via the combination of TEMPO mediated and anionic polymerisation[116]. Brushes were also prepared by the functionalisation of a pre-prepared polymer backbone to form pendant alkoxyamine macroinitiator residues, which were then used to grow polystyrene side arms in a controlled fashion[117].

The synthesis of star shaped polymers has been demonstrated by a number of groups. The use of multifunctional initiators to form styrene branch stars[118] [Figure 86].

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[112] Hawker, Macromolecules, **1996**, 29, 2686-2688

[113] Lokaj, Journal of Applied Polymer Science, **2000**, 76, 1093-1099

[114] Kazmaier, P.M., Daimon, K., Georges, M.K., Hamer, G.K., Veregin, R.P.N., Macromolecules, **1997**, 30, 2228-2231

[115] Lacroix-Desmazes, P., Delair, T., Pichot, C., Boutevin, B., Journal of Polymer Science: Part A, Polymer Chemistry, **2000**, 38, 3845-3854

[116] Tsoukatos, T., Pispas, S., Hadjichristidis, N., Macromolecules, **2000**, 33, 9504-9511

[117] Sun, Y., Wan, D., Huang, J., Journal of Polymer Science: Part A Polymer Chemistry, **2001**, 39, 604-612

[118] Hawker, C.J., Angew. Chem. Int. Ed. Engl., **1995**, 34, 1456-1459

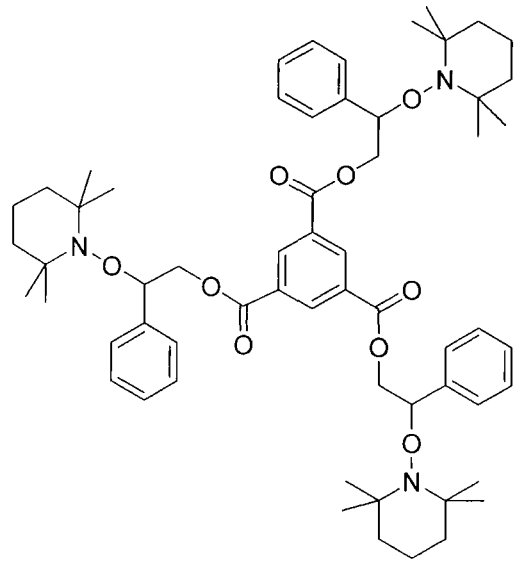


Figure 86 Multifunctional initiators for star synthesis

The use of multifunctional initiators based on the SG1 nitroxide to prepare star polymers has been demonstrated for polystyrene and polybutyl acrylate homoarm and block copolymer arm stars[119] [Figure 87].

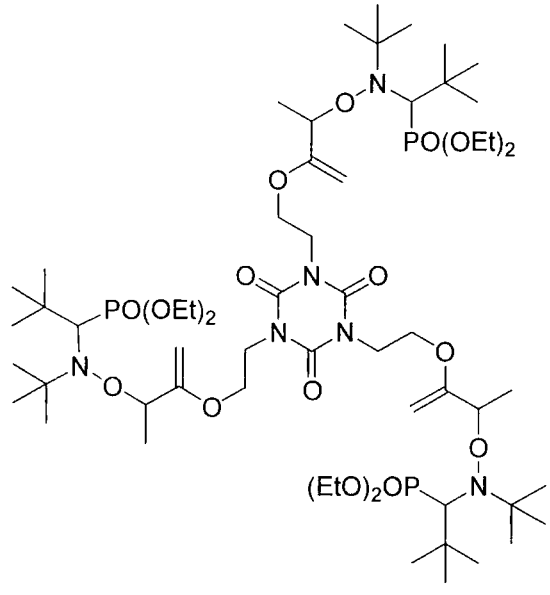
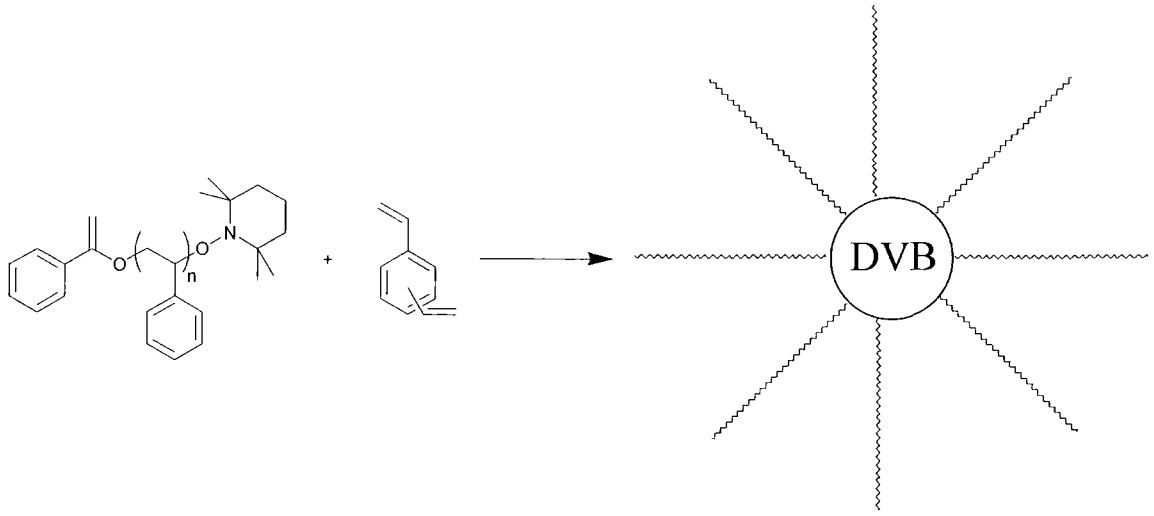


Figure 87 Multifunctional initiators from SG1 for star synthesis

[119] Robin, S.,Guerret, O., Couturier, J.-L., Gnanou, Y., Macromolecules, **2002**, 35, 2481-2486

Star shaped polymers have also been prepared by the coupling of a TEMPO



alkoxyamine terminated macroinitiator with divinyl benzene[120] [Figure 88].

Figure 88 Star shaped polymers from alkoxyamine terminated macroinitiator with divinyl benzene

A similar work extended this by synthesising a star polymer by the reaction of TEMPO alkoxyamine terminated polystyrene with divinyl benzene. The resulting polymer was used as a macroinitiator with the TEMPO alkoxyamine terminated core initiating styrene polymerisation, which resulted in an asymmetric (or miktoarm) star homopolymer[121].

Surface initiated polymerisation has been demonstrated by Hawker[122] through the functionalisation of a silicon substrate to form an alkoxyamine. This was used to

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[120] Pasquale, A.J., Long, T.E., Journal of Polymer Science Part A Polymer Chemistry, **2001**, 39, 216-223

[121] Tsoukatos, T., As, S., Hadjichristidis, N., Journal of Polymer Science: Part A Polymer Chemistry, **2001**, 39, 320-325

[122] Husemann, M., Morrison, M., Benoit, D., Frommer, J., Mate, C.M., Hinsberg, W.D., Hedrick, J.L., Hawker, C.J., J. Am. Chem. Soc., **2000**, 122, 1844-1845

grow a well defined poly(butyl acrylate) brush through controlled radical polymerisation.

Dispersed Phase Controlled Radical Polymerisation

The water tolerance of controlled radical polymerisations has allowed the study of these systems in dispersed media such as suspension[123], emulsion or more commonly miniemulsion[124-127].

Initiating systems employed have been based on TEMPO, a TEMPO terminated macroinitiator and more promisingly SG1 nitroxide, which allows lower polymerisation temperature to be used. These have also been used in the preparation of acrylate homo- and acrylate/styrene block copolymers [129]

Summary

A number of techniques for the control of radical polymerisation have been developed offering the prospect of tailored and novel macromolecular structures via synthetically robust routes. ATRP, RAFT and nitroxide mediated polymerisation have been the subject of much research in both academia and industry and look to be the subject of further work for some time to come.

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[123] Schmidt-Naake, G., Drache, M., Taube, C., Angewandte Makromolecular Chemie, **1999**, 265, 62-68

[124] Butté, A., Stort, G., Morbidelli, M., Macromol., **2000**, 33, 3485-3487

[125] Farcet, C., Lansalot, M., Charleux, B., Pirri, R., Vairon, J-P., Macromol., **2000** ,33 ,8559-8570

[126] Pan, G., Sudol, E.D., Dimonie, V.L., El-Asser, M.S., Macromol, **2001**, 34, 481-488

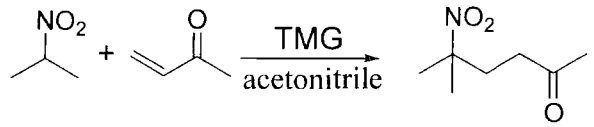
[127] Cunningham, M.F., Xie, M., McAuley, K.B., Keoshkerian, B., Georges, M.K., Macromol, **2002**, 35, 59-66

[128] Charleux, B., Macromolecules, **2000**, 33, 5358-5365

[129] Farcet, C., Charleux, B., Pirri, R., Macromol., **2001**, 34, 3823-3826

Chapter 2 - Synthesis

5-Methyl-5-nitro-hexan-2-one nitroketone synthesis



2-Nitropropane (24.4g, 0.27mol) and methyl vinyl ketone (17.5g, 0.25mol) were dissolved in acetonitrile (160ml) and placed in a round-bottomed flask. The solution was then cooled over crushed ice. Tetramethyl guanidine (2.88g, 25mmol) was added dropwise with stirring over a period of ten minutes. The cooling ice was then removed and the mixture allowed to slowly reach room temperature. The reaction mix was then stirred overnight before being quenched by addition of dilute hydrochloric acid solution (1l, 0.06M). The resulting solution was extracted three times with diethyl ether. The organic extracts were then combined and dried with magnesium sulfate. The dried extracts were filtered through a fluted filter paper and placed on a rotary evaporator to remove solvent. A greater than 100% crude yield was obtained and no further purification carried out.

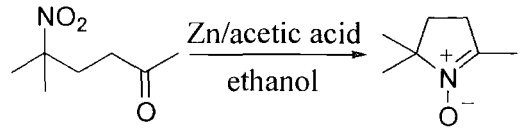
^{1}H NMR (300MHz): δ= 1.55 (s, 6H, $(C\underline{H}_3)_2CNO_2$), 2.14 (s, 3H, $C\underline{H}_3CO$), 2.18 (t, J=8.5Hz, 2H, $C\underline{H}_2CNO$), 2.45 (t, J=8.5Hz, 2H, $C\underline{H}_2CO$) ppm.

The proton NMR spectra obtained is in agreement with literature analytical data[130].

[130] Ono, N., Kamimura, A., Miyake, H., Hamamoto, Kaji, J. Org. Chem. **1985**, 50, 3692

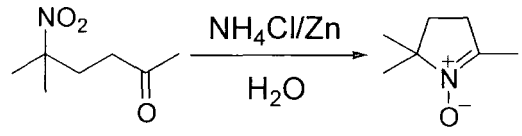
Reductive cyclisation of 5-methyl-5-nitro-2-hexanone to form 2,2,5 trimethylpyrrolidin-N-oxide

a) Nitrone synthesis, zinc dust acetic acid route



Crude 5-methyl-5-nitro-2-hexanone (40g, 0.25mol) prepared as described above was dissolved in ethanol (300ml). Zinc dust (6.54g, 0.1mole) was added after which glacial acetic acid (20ml) added dropwise with stirring. After stirring overnight the residual zinc metal was removed from the resulting reaction mixture by filtration through a buchner funnel. Solvent was then removed by rotary evaporation. Removal of the last traces of acetic acid from the resulting crude material proved to be problematic and no usable product was obtained.

b) Nitrone synthesis, Ammonium chloride/ Zinc dust route



5-Methyl-5-nitro-2-hexanone crude (40g, 0.25mol) prepared as described above was mixed with water (160ml) and ammonium chloride (17.6g, 0.33mol). The resulting mixture was then cooled to $-10^{o}C$ over a crushed ice/salt mixture and activated zinc dust (40g, 0.61mol) added in small portions with stirring over a period of two hours. Immediately prior to use zinc dust was activated by removal of surface oxides. This was achieved by stirring zinc (40g, 0.61mol) with 10ml of 10% hydrochloric acid solution for two minutes. The zinc dust was then filtered over a buchner funnel and washed with 30ml of water followed by 10ml of acetone and allowed to dry.

The solution obtained after addition of zinc dust was stirred for a further half hour before filtering on a buchner funnel, and the remaining solids washed through with a

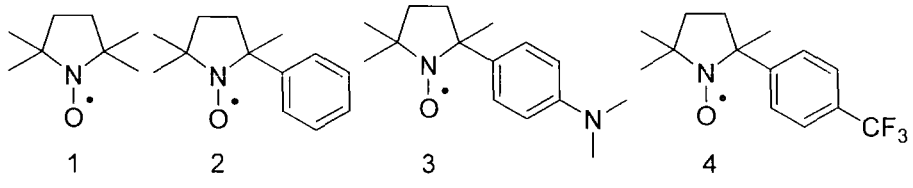
small quantity of methanol. The organic products were removed from the resulting water mixture by extraction with three portions of dichloromethane. The dichloromethane extracts were then combined, dried with magnesium sulfate, filtered through a fluted filter paper and solvent removed using a rotary evaporator. The resulting 2,2,5-trimethylpyrrolidin-N-oxide was stored in the refrigerator and distilled under vacuum as required. Yields of this reaction varied considerably depending on the success of the vacuum distillation purification step and typically 7 to 10g of usable material were obtained resulting in yields in the order of 25-30%.

^{1}H NMR (300MHz): δ= 1.40 (s, 6H, $C(C\underline{H}_3)_2$), 2.02 (m, 2H, $C(CH_3)C\underline{H}_2$), 2.05 (s, 3H, $C\underline{H}_3CN$), 2.60 (m, 2H, $C\underline{H}_2CN$) ppm.

The proton NMR spectra is in agreement with analytical data presented elsewhere[131] and further characterisation was not deemed necessary.

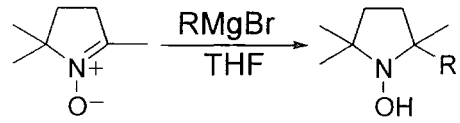
Nitroxide syntheses

A series of nitroxides, 2,2,5,5-tetramethylpyrrolidine-N-oxyl **1**, 2,5,5-trimethyl-2-phenylpyrrolidine-N-oxyl **2**, 2,5,5-trimethyl-2-*para*-N,N-dimethylanilinepyrrolidine-N-oxyl **3** and 2,5,5-trimethyl-2-*para*-trifluoromethylphenylpyrrolidine-N-oxyl **4** were prepared via a common synthetic route and a generic synthesis is described for these compounds.



[131] Turner, M.J., Luckenbach, L.A., Turner, E.L., Synth. Commun., **1986**, 16, 1377

Hydroxylamine synthesis

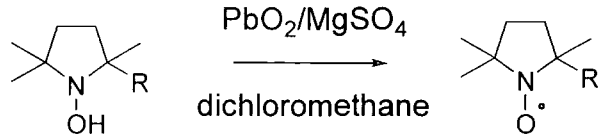


2,2,5-Trimethylpyrrolidin-N-oxide prepared as described above was freshly distilled under vacuum from the crude immediately prior to use. For each nitroxide the appropriate Grignard reagent was either transferred under argon via cannula into a dry round bottomed flask fitted with a water condenser and septum or prepared in-situ and cooled over an ice bath. Nitroxide **1** was prepared with methyl magnesium bromide (14ml, 3M, 42mmol) as supplied by Aldrich. Nitroxide **2** was prepared using phenyl magnesium bromide (40ml, 1M, 40mmol) as supplied by Aldrich. Nitroxide **3** was prepared using a Grignard reagent generated by stirring magnesium (2.12g, 88mmol) under argon and adding a solution of *p*-bromo-N,N-dimethyl aniline (12.4g, 62mmol) dissolved in THF from a dropping funnel. Nitroxide **4** was prepared with a Grignard reagent generated by stirring magnesium (1.086g, 44mmol) under argon and adding a solution of 1-bromo-4-trifluoromethylbenzene (6.9019g, 30.67mmol) dissolved in THF slowly from a dropping funnel.

To the appropriate Grignard solution 2,2,5-trimethylpyrrolidin-N-oxide (2.54g, 20mmol) was added slowly by syringe with stirring. After the reaction appeared to have ceased the ice was removed and the mixture allowed to slowly warm to room temperature. Excess Grignard reagent was then quenched by the slow addition of saturated ammonium chloride solution (40ml). The reaction mixture was then exposed to the air and any solids formed in the solution dissolved by the addition of a small volume of water. The organic and aqueous layers were then separated and the aqueous layer extracted three times with diethyl ether. The organic extracts were combined, dried over magnesium sulfate, filtered through a fluted filter paper and the

resulting solution placed on the rotary evaporator to remove solvent and leave crude hydroxylamine.

Hydroxylamine oxidation



Crude hydroxylamine prepared as described above was dissolved in dichloromethane (50ml). Lead oxide (2g, 0.0084mol) and dried magnesium sulfate were added and the mixture stirred for one hour. The resulting solution was filtered through a fluted filter paper and solvent removed on a rotary evaporator. The resulting materials were purified by flash chromatography with 90:10 40-60° petroleum ether: ethyl acetate eluant.

Nitroxide	Purified Yield
1	25%
2	36%
3	20%
4	25%

Nitroxide **1** – analytical data was in agreement with literature data[132]

Nitroxide **2** – analytical data was in agreement with literature data[133]

Nitroxide **3** - $C_{15}H_{23}N_2O$ (247.3595)

Calc. C 72.84 H 9.37 N 11.32

[132] Hideg, K., Hankovszky, H.O., Halasz, H.A., Sohar, P., J. Chem. Soc., Perkin Trans.1, **1988**, 2905

[133] Couet, W.R., Brasch, R.C., Sosnovsky, G., Lukszo, J., Prakash, I., Gnewuch, C.T., Tozer, T.N., Tetrahedron, **1985**, 41, 1165

Found C 72.51 H 9.29 N 11.23

^{1}H NMR (400Hz): δ=1.21 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.55 (s, 3H, CH_3 adj. To Ar), 1.69-1.83 (m, 2H, $(H_3C)_2CC\underline{H}_2$), 1.90-2.05 (m, 2H, $(H_3C)(Ar)CC\underline{H}_2$), 2.88 (s, 6H, $N(CH_3)_2$), 6.65 (d, J= 9Hz, 2H, *o*-$N(CH_3)_2$), 7.42 (d, J= 9Hz, 2H, *m*-$N(CH_3)_2$) ppm

13C NMR (100Hz): δ=22.2, 23.7, 29.8 (CH_3 x 3), 35.4 ($\underline{C}H_2$-$C(CH_3)_2$), 36.8 ($\underline{C}H_2$-$C(CH_3)(Ar)$, 40.5 ($N(CH_3)_2$), 64.2 ($\underline{C}(CH_3)_2$), 68.8 ($\underline{C}(CH_3)(Ar)$), 112.6 (aryl $\underline{C}H$ *o*-$N(CH_3)_2$), 127.2 (aryl $\underline{C}H$ *m*-$N(CH_3)_2$), 143.2 (aryl C), 149.0 (aryl $\underline{C}$-$N(CH_3)_2$) ppm

MS (EI) *m/z* 247 ($[M]^+$, 11), 161 (100)

Nitroxide **4** - $C_{14}H_{17}F_3NO$ (272.2896)

Calc. C 61.76 H 6.29 N 5.14 F 20.93

Found C 61.63 H 6.26 N 5.05 F 20.92

^{1}H NMR (400 MHz): δ= 1.23 (s, 3H, CH_3), 1.26 (s, 3H, CH_3), 1.53 (s, 3H, CH_3 adj. To Ar), 1.60-1.80 (m, 2H, $(H_3C)_2CC\underline{H}_2$), 1.86-2.06 (m, 2H, $(H_3C)(Ar)CC\underline{H}_2$), 7.50 (m, 2H, *m*-$CF_3$), 7.62 (m, 2H, *o*-$CF_3$) ppm

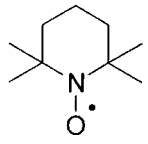
^{13}C NMR (100Hz): δ= 22.5, 22.9, 29.6 (CH_3 x 3), 35.0 ($\underline{C}H_2$-$C(CH_3)_2$), 37.6 ($\underline{C}H_2$-$C(CH_3)(Ar)$, 63.5 ($\underline{C}(CH_3)_2$), 68.0 ($\underline{C}(CH_3)(Ar)$, 124.4 (q, $^1J_{13C,19F}$ = 272Hz, CF_3), 124.8 (q, $^3J_{13C,19F}$ = 32Hz, aryl $\underline{C}H$ *o*-CF_3), 126.1 (aryl $\underline{C}H$ *m*-CF3), 128.1 (q, $^2J_{13C,19F}$ = 32Hz, aryl $\underline{C}$-CF_3), 154.3 (aryl C) ppm

MS (EI) *m/z* 273 ($[M+1]^+$,25), 186 (100)

Alkoxyamine Synthesis

A series of alkoxyamines, 2-*tert*-butoxy-1-phenyl-1-(1-oxy-2,2,6,6-tetramethylpiperidinyl)ethane, **6**, 2-*tert*-butoxy-1-phenyl-1-(1-oxy-2,2,5,5-tetramethyl-pyrrolidinyl)ethane, **7**, 2-*tert*-butoxy-1-phenyl-1-(1-oxy-2,5,5-trimethyl-

2-phenyl-pyrrolidinyl)ethane, **8**, 2-*tert*-butoxy-1-phenyl-1-(1-oxy-2,5,5-trimethyl-2-*para*-N,N-dimethylaniline-pyrrolidinyl)ethane, **9,** and 2-*tert*-butoxy-1-phenyl-1-(1-oxy-2,5,5-trimethyl-2-*para*-trifluoromethylphenyl-pyrrolidinyl)ethane, **10,** were prepared from the 2,2,6,6-tetramethylpiperidine-N-oxyl, TEMPO, nitroxide, **5**, obtained from Aldrich and nitroxides **1-4** prepared as previously described. As the synthesis of these alkoxyamines is general, with the exception of the nitroxide used, a generic synthesis is described followed by details of yields and analytical data for the individual alkoxyamines.



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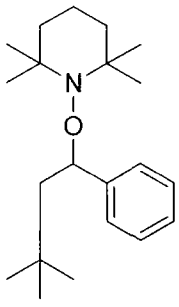

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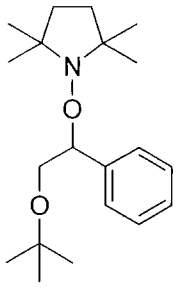

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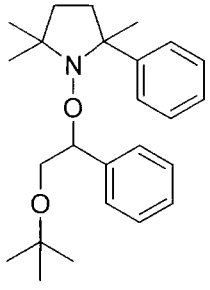

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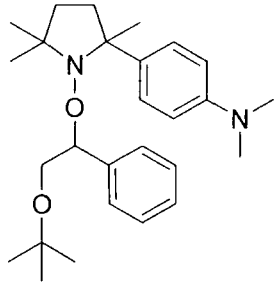

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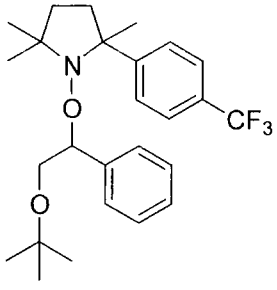
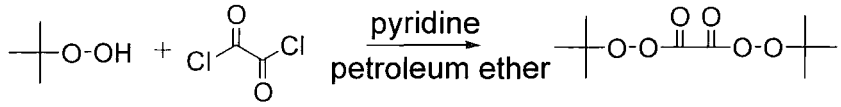


10

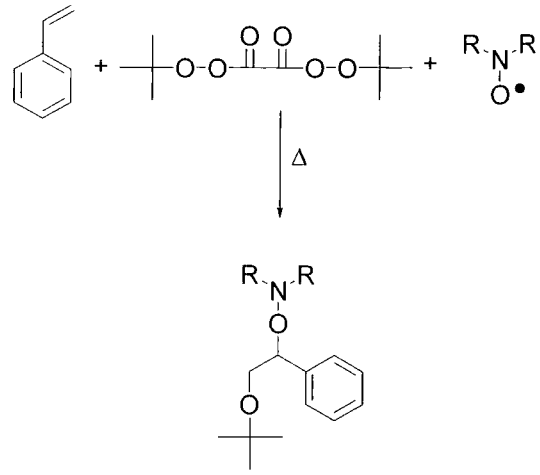
Di-*tert*-butyl peroxalate (DTBPO) synthesis



Tert-butyl hydroperoxide (1.2ml, 6mmol) and pyridine (0.6ml) were dissolved in 40-60° petroleum ether (6ml), placed in a round-bottomed flask which was then sealed with a septum, flushed with argon and cooled over a dry ice/acetone slush bath. A solution of oxalyl chloride (0.3ml, 3.5mmol) dissolved in petroleum ether (4ml) was then added dropwise via syringe over ten minutes. After one and a half hours the dry ice/acetone slush cooling bath was removed from below the reaction and the reaction mixture allowed to warm slowly to room temperature. The white solid formed was removed by filtration through a buchner funnel and the resulting solution was again cooled over a dry ice/acetone slush bath causing a precipitate to form. This was collected by filtration on a buchner funnel but not allowed to dry completely. This precipitated product was either used immediately or stored in a plastic bottle and placed in the freezer for later use.

Note: Extreme care should be taken in the preparation and handling of DTBPO as it may undergo an explosive decomposition upon drying or in contact with metallic surfaces and is percussion sensitive.

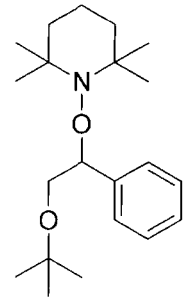
Alkoxyamine synthesis



A solution of the appropriate nitroxide (1.2mmol) and di-*tert*-butyl peroxalate (0.1481g, 0.633mmol) was made up in styrene (5ml). The mixture was degassed by three freeze/pump/thaw cycles and backflushed with argon. The resulting solution was heated overnight at 40°C. After cooling the solution was dried under vacuum to remove styrene. The solids obtained were then purified by flash chromatography eluting with a 40-60° petroleum ether/ethyl acetate mix.

2-*Tert*-butoxy-1-phenyl-1-(1-oxy-2,2,6,6-tetramethylpiperidinyl)ethane,

alkoxyamine **6**

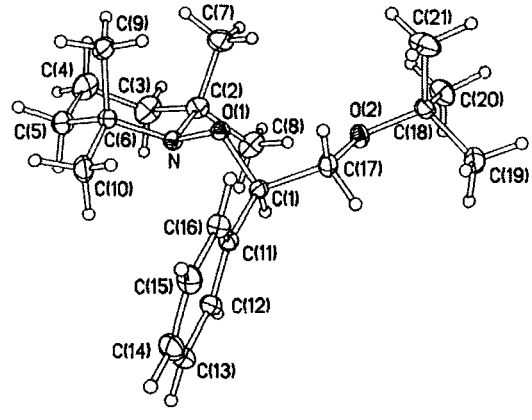


A white crystalline solid was obtained (0.1880g, 1.21mmol) in 79% yield. The isolated product was identified by NMR and is in agreement with analysis described in the literature [134].

$C_{21}H_{35}NO_2$

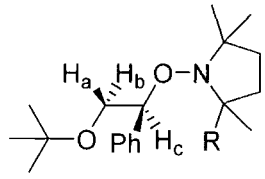
^{1}H NMR (300MHz): δ= 1.04 (s, 9H, CH_3 x 3), 0.58, 1.02, 1.19, 1.37 (br s, 3H, CH_3), 0.9-1.7 (br m, 6H, CH_2 x3), 3.41 (m, 1H, H_a), 3.89 (m, 1 H, H_b), 4.74 (m, 1H, H_c), 7.18-7.35 (m, 5H, Ph) ppm

A crystal structure of this material was obtained and is presented in full as an appendix.

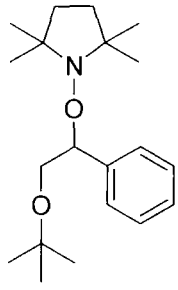


[134] Bon, S.A.F., Chambard, G., German, A.L., Macromolecules, **1999**, 32, 8269-8276

In the interpretation of subsequent diastereomeric alkoxyamines **7-10** styryl protons are assigned accordingly.



2-*Tert*-butoxy-1-phenyl-1-(1-oxy-2,2,5,5-tetramethyl-pyrrolidinyl)ethane, alkoxyamine **7**



The pure product was obtained as a pale straw coloured oil (0.1750g, 1.23mmol) in 71% yield.

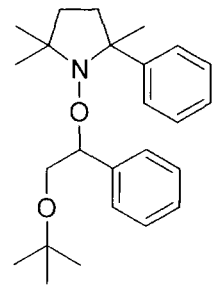
$C_{20}H_{33}NO_2$ (319.4862)	Calculated	C 75.24 H 10.34 N 4.38
	Found	C 75.33 H 9.97 N 3.39

^{1}H NMR (300 MHz): δ = 0.43, 0.95, 1.16, 1.27 (s, 12H, CH_3 x 4), 1.10 (s, 9H, $(CH_3)_3C$), 1.50 (br s, 4H, CH_2 x 2), 3.25 (dd, J_{gem}= 11 Hz, J_{cis}= 2 Hz, 1H, H_b), 3.67 (dd, J_{gem}= 16 Hz, J_{trans}= 9 Hz, J_{cis}= 2 Hz, 1H, H_a), 4.59 (dd, J_{trans}= 9 Hz, J_{cis}=2 Hz, 1H, H_c), 7.10-7.40 (m, 5H, Ph) ppm

^{13}C NMR (75 MHz): δ = 23.0, 24.6, 30.9, 31.2 (CH_3 x 4), 27.7 ($(CH_3)_3\underline{C}$), 35.8, 36.2 (CH_2 x 2), 63.3, 65.2 ($\underline{C}(CH_3)_2$ x 2), 65.6 ($\underline{C}H_aH_b$), 73.2 ($(CH_3)\underline{C}$-O), 87.7 ($\underline{C}H_c$-Ph), 127.6, 128.0, 128.1 (aryl CH), 142.5 (aryl C) ppm

MS (EI): *m/z* = 319 $[M]^+$, 177, 143 [Nitroxide$^+$ +1], 128, 104

2-*Tert*-butoxy-1-phenyl-1-(1-oxy-2,5,5-trimethyl-2-phenyl-pyrrolidinyl)ethane alkoxyamine **8**



The pure product was obtained as a pale straw coloured oil (0.2614g, 1.28mmol) in 82% yield.

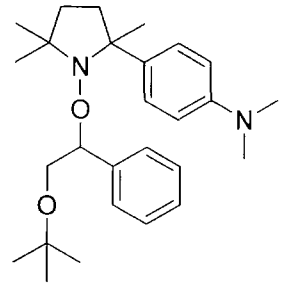
$C_{25}H_{35}NO_2$ (381.5573)	Calculated	C 78.74 H 9.19 N 3.67
	Found	C 78.87 H 9.15 N 3.59

^{1}H NMR (200 MHz): δ = 0.72, 1.10, 1.29, 1.42, 1.49, 1.68 (s, 18H, CH_3 x 3, both diastereomers), 0.85, 1.05 (s, 18H, $(CH_3)_3C$, both diastereomers), 1.40-2.00 (m, 8H, CH_2 x 2, both diastereomers), 2.95, 3.25 (dd, J_{gem}= 10Hz, J_{cis}= 6 Hz, 2H, H_b, both diastereomers), 3.30, 3.62 (dd, J_{trans}= 7 Hz, 2H, H_a, both diastereomers), 4.20, 4.40 (dd, J_{trans}= 7 Hz, J_{cis}= 5 Hz 2H, H_c, both diastereomers), 6.80-7.70 (m, 20H, Ar-CH, both diastereomers) ppm.

^{13}C DEPT NMR (100 MHz): δ = 22.5, 23.0, 23.2, 26.1, 29.6, 30.1 (CH_3 x 3, both diastereomers), 27.2, 27.4 ($(CH_3)_3\underline{C}$, both diastereomers), 36.0, 36.2 ($\underline{C}H_2$-$C(CH_3)_2$, both diastereomers), 39.9, 40.2 ($\underline{C}H_2$-$C(CH_3)$(Ph), both diastereomers), 64.2, 65.2 ($\underline{C}(CH_3)_2$, $\underline{C}H_2$-$C(CH_3)_2$, both diastereomers), 64.7, 65.1 (CH_aH_b, both diastereomers), 68.2, 68.7 ($\underline{C}(CH_3)$(Ph), both diastereomers), 72.8, ($(CH_3)\underline{C}$-O, both diastereomers), 84.7, 85.7 (CH_c-Ph, both diastereomers), 125.0-129.0 (aryl CH x 6, both diastereomers), 141.0, 141.7 (aryl $\underline{C}$-CH_c, both diastereomers), 150.4, 151.4 (aryl $\underline{C}$-$C(CH_3)$, both diastereomers) ppm.

MS (EI): *m/z* = 381 $[M]^+$, 205 [Nitroxide$^+$ +1], 190, 104

2-*Tert*-butoxy-1-phenyl-1-(1-oxy-2,5,5-trimethyl-2-*para*-N,N-dimethylaniline-pyrrolidinyl)ethane, alkoxyamine **9**



Very small, variable, quantities of rose coloured crystal were obtained (0.33g, 1.35mmol) which turned to brown oil overnight possibly due to the absorption of water from the atmosphere which may account for the poor results of elemental analysis although NMR analysis would suggest that the desired product is indeed obtained. Typical yields ranged from 10-15%

$C_{27}H_{40}N_2O_2$ (424.6252)	Calculated	C 76.40 H 9.43 N 6.60
	Found	C 75.54 H 9.42 N 6.37

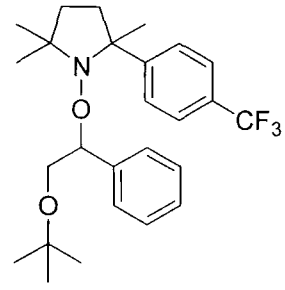
^{1}H NMR (200 MHz): δ = 0.72, 1.10, 1.29, 1.38, 1.48, 1.62 (s, 18H, CH_3 x 3, both diastereomers), 0.86, 1.03 (s, 18H, $(CH_3)_3C$, both diastereomers), 1.35-1.90 (m, 8H, CH_2 x 2, both diastereomers), 2.82, 2.87 (s, 12H, $-N(CH_3)_2$, both diastereomers), 2.95, 3.25 (dd, J_{gem} = 10 Hz, J_{cis} = 6 Hz 2H, H_b, both diastereomers), 3.30, 3.62 (dd, J_{gem} = 10 Hz, J_{trans} = 9 Hz, 2H, H_a, both diastereomers), 4.23, 4.38 (dd, J_{trans} = 10 Hz, J_{cis} = 6 Hz, 2H, H_c, both diastereomers), 6.41 (d), 6.68 (d), 6.93 (d), 7.05 - 7.30 (m), 7.42 (d) (18H, Ar-CH, both diastereomers) ppm.

^{13}C NMR (75 MHz): δ = 22.5, 22.9, 23.8, 28.8, 30.3, 30.7 (CH_3 x 3, both diastereomers), 27.6, 27.7 ($(CH_3)_3\underline{C}$, both diastereomers), 36.5, 36.8 ($\underline{C}H_2$-$C(CH_3)_2$,

both diastereomers), 39.8, 40.0 ($\underline{C}H_2$-$C(CH_3)(Ar)$, both diastereomers), 41.2 ($N(CH_3)_2$, both diastereomers (overlapping peaks)), 64.2, 65.0 ($\underline{C}(CH_3)_2$, $\underline{C}H_2$-$C(CH_3)_2$, both diastereomers), 64.9, 65.3 (CH_aH_b, both diastereomers), 68.3, 68.5 ($\underline{C}(CH_3)(Ar)$, both diastereomers), 73.0 ($(CH_3)\underline{C}$-O, both diastereomers (overlapping peaks)), 84.6, 85.4 (CH_c-Ph, both diastereomers), 112.6 (aryl $\underline{C}H$ *o*-$N(CH_3)_2$, both diastereomers (overlapping peaks)), 125.0-129.0 (aryl $\underline{C}H$ *m*-$N(CH_3)_2$ and Ph $\underline{C}H$ x 3, both diastereomers), 139.4, 139.8 (aryl $\underline{C}$ *p*-$N(CH_3)_2$, both diastereomers), 141.5, 142.2 ($\underline{C}$-CH_c), both diastereomers), 149.0, 149.3 (aryl $\underline{C}$-$N(CH_3)_2$), both diastereomers) ppm.

MS (EI): m/z = 424 $[M]^+$, 312, 256, 247 $[\text{Nitroxide}]^+$

2-*Tert*-butoxy-1-phenyl-1-(1-oxy-2,5,5-trimethyl-2-*para*-trifluoromethylphenyl-pyrrolidinyl)ethane, alkoxyamine **10**



10

A pale yellow/green solid was obtained (0.7011g, 2.58mmol) in 38% yield. While NMR and mass spectroscopy evidence suggest that this product is indeed obtained poor results were seen for elemental analysis possibly due to absorption of water or some degradation of the sample prior to analysis.

$C_{26}H_{34}F_3NO_2$ (449.5556)	Calculated	C 69.49 H 7.50 N 3.10
	Found	C 68.38 H 6.47 N 2.01

^{1}H NMR (200 MHz): δ = 0.72, 1.10, 1.29, 1.42, 1.49, 1.68 (s, 18H, CH_3 x 3, both diastereomers), 0.85, 1.05 (s, 18H, $(CH_3)_3C$, both diastereomers), 1.40-2.00 (m, 8H, CH_2 x 2, both diastereomers), 2.95, 3.25 (dd, J_{gem} = 10 Hz, J_{cis} = 3 Hz, 2H, H_b, both diastereomers), 3.30, 3.62 (dd, J_{gem} = 8 Hz, J_{trans} = 7 Hz, 2H, H_a, both diastereomers), 4.20, 4.40 (dd, J_{trans} = 7 Hz, J_{cis} = 4 Hz, 2H, H_c, both diastereomers), 6.80-7.70 (m, 18H, Ar-CH, both diastereomers) ppm.

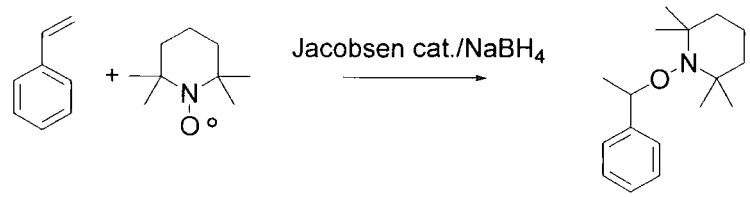
^{13}C DEPT NMR (100 MHz): δ = 22.5, 22.9, 23.2, 26.1, 29.7, 30.6 (CH_3 x 3, both diastereomers), 27.1, 27.4 ($(CH_3)_3\underline{C}$, both diastereomers), 35.7, 36.2 ($\underline{C}H_2$-$C(CH_3)_2$, both diastereomers), 39.8, 40.2 ($\underline{C}H_2$-$C(CH_3)$(Ar), both diastereomers), 64.5, 65.4 ($\underline{C}(CH_3)_2$, $\underline{C}H_2$-$C(CH_3)_2$, both diastereomers), 64.8, 65.5 (CH_aH_b, both diastereomers), 67.8, 68.7 ($\underline{C}(CH_3)$(Ar), both diastereomers), 72.8 ($(CH_3)\underline{C}$-O, both diastereomers), 85.1, 87.2 (CH_c-Ph, both diastereomers), 125.0-129.0 (aryl CH x 2,

Ph CH x 3, CF_3 and C-CF_3, both diastereomers), 141.4, 143.2 (C-CH_c, both diastereomers), 154.3, 155.7 (C-C(CH_3), both diastereomers) ppm.

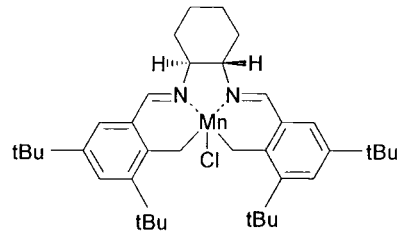
MS(EI): *m/z* = 450 $[M]^+$, 290, 272 $[Nitroxide]^+$

Catalytic synthesis of alkoxyamines using Jacobsen's catalyst

1-Phenyl-1-(1-oxy-2,2,6,6-tetramethylpiperidinyl)ethane, Alkoxyamine **11**



11



Jacobsen's Catalyst

A solution of styrene (1g, 9.6mmol) and TEMPO (0.97g, 6.2mmol) was made up in 100ml of a 1:1 ratio of toluene and ethanol. Mn(III) complex (Jacobsen's catalyst) (1.1g, 1.7mmol), di-*tert*-butyl peroxide (0.91g, 6.2mmol) and sodium borohydride (0.71g, 19mmol) were added and air bubbled through the resulting solution with stirring overnight. Solvent was removed from the resulting solution on a rotary evaporator. After removal of volatiles the resulting material was dissolved in dichloromethane (50ml) and washed with water. The dichloromethane solution was then placed on the rotary evaporator to remove solvent. The crude material was purified by flash chromatography eluting 95/5 petroleum ether/ethyl acetate mixture with a very small amount of isopropyl alcohol.

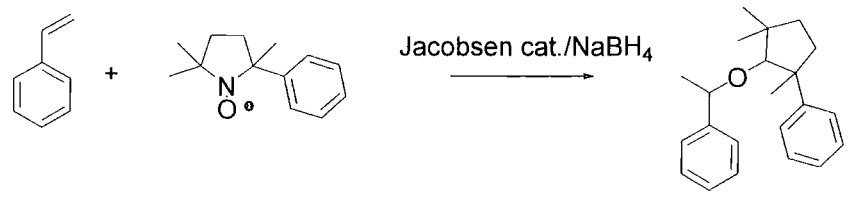
Alkoxyamine **11** was obtained as a white powdery solid (0.43g, 1.65mmol), 27% yield.

^{1}H NMR (200 MHz): δ = 0.64, 1.05, 1.16, 1.36 (br s, 12 H, C$\underline{H}_3$), 1.23-1.58 (m, 6H, C$\underline{H}_2$), 1.44 (d, J = 7 Hz, 3H, CH(C$\underline{H}_3$)), 4.76 (q, J = 7 Hz, 1H, C$\underline{H}$(CH$_3$)), 7.25-7.35 (m, 5H, ArH) ppm.

The proton NMR spectra is in agreement with literature analysis[135] and no further characterisation was performed.

[135] Hawker, C.J., Barclay, G.G., Orellano, A., Dao, J., Macromolecules, **1996**, 29,

1-Phenyl-1-(1-oxy-2,2,5,5-tetramethyl-pyrrolidinyl)ethane, alkoxyamine **12**



12

A solution of styrene (1g, 9.6mmol) and 2,2,5-trimethyl-5-phenylpyrrolidine-N-oxyl nitroxide (1.26g, 6.2mmol) was made up in 1:1 toluene/ethanol. Mn(III) complex (Jacobsen's catalyst) (1.1g, 1.7mmol), di-*tert*-butyl peroxide (0.91g, 6.2mmol) and sodium borohydride (0.71g, 19mmol) were added and the air bubbled through the resulting solution with stirring at room temperature overnight. Solvent was removed from the resulting solution by placing it on a rotary evaporator. The remaining material was dissolved in dichloromethane (50ml) and separated from water. The dichloromethane solution was then placed on the rotary evaporator. The crude product was then purified by flash chromatography eluting 95/5 petroleum ether/ethyl acetate with a small amount of isopropyl alcohol mix.

The product (0.47g, 1.52mmol) was obtained as a pale yellow oil, 25% yield. A slight discrepancy exists for carbon in elemental analysis although NMR and mass spectroscopy data suggest the formation of the desired product.

$C_{21}H_{27}NO$	Calculated	C 81.55% H 8.74% N 4.53%
	Found	C 80.93% H 8.82% N 4.25%

^{1}H NMR (200 MHz): δ = 0.67, 1.00, 1.05, 1.10, 1.43, 1.50, 1.59 (9H s, C<u>H</u>$_3$ x 3, both diasteromers,), 1.37 (d, 3H, C<u>H</u>$_3$CH, both diastereomers (overlapping peaks)), 1.63-1.95 (m, 4H, C<u>H</u>$_2$, both diastereomers), 4.21 (m, 1H CH$_3$C<u>H</u>, both diastereomers (overlapping peaks)), 6.90-7.61 (m, 5H, aryl H, both diastereomers)

^{13}C DEPT NMR (100 MHz): δ = 22.2, 22.3, 22.8, 22.9, 23.5, 23.6, 29.9, 30.0 (CH_3 x 4, both diastereomers), 38.2, 38.3 ($\underline{C}H_2C(CH_3)_2$) both diastereomers), 40.2, 40.3 ($\underline{C}CH_2C(CH_3)$(Ar) both diastereomers), 64.1, 64.3 ($\underline{C}(CH_3)_2$ both diastereomers), 68.1, 68.2 ($\underline{C}(CH_3)$(Ar) both diastereomers), 79.8, 81.3 ($CH_3\underline{C}H$ both diastereomers), 125-130 (aryl CH x 6 both diastereomers), 144.0, 145.3 (aryl CCH(CH3) both diastereomers), 152.7, 152.8 (aryl $CC(CH_3)$ both diastereomers)

MS (EI): *m/z* = 309[M +1], 205, 190, 131, 118, 105, 91, 77

Chapter 3 - Styrene Polymerisation

Introduction

The practical demonstration by Georges *et al.*[136] of controlled radical polymerisation through the reversible capping of transient propagating radicals with a stable nitroxide radical [Figure 89], as originally patented by Rizzardo *et al.*[137], has led to significant interest from both industry and academia. Nitroxide mediated controlled radical polymerisation has since been developed and applied by a number of groups alongside RAFT and ATRP controlled radical polymerisation methodologies as a synthetically robust method of achieving macromolecular structural control.

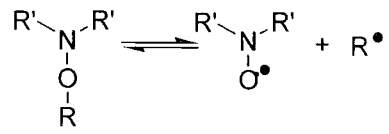


Figure 89 Reversible capping of transient radical by nitroxide

Controlled radical polymerisations mediated by nitroxide stable radicals have been shown to display several features normally considered characteristic of living polymerisations such as an increase in molecular weight with conversion and the formation of a low polydispersity product which is able to undergo further chain extension. Initial investigations into nitroxide mediation of radical polymerisation made use of a bimolecular initiating system of TEMPO, 2,2,6,6-tetramethylpiperidin-N-oxyl nitroxide as mediating species in conjunction with a conventional radical initiator. Subsequent work[138] has demonstrated similar features using unimolecular

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[136] Georges, M.K., Veregin, R.P.N., Kazmaier, P.M., Hamer, G.K., Macromolecules, **1993**, 26, 2987-2988

[137] Solomon, D.H., Rizzardo, E., Caclioli, P., EP0135280, US 4,581,429

[138] Hawker, C.J., J. Am. Chem. Soc., **1994**, 116, 11185-11186

alkoxyamine initiators which have been shown to undergo homolysis of the alkoxyamine carbon to oxygen bond under polymerisation conditions to generate a stable mediating nitroxide radical and an initiating radical. Later studies[139] showed that the use of alkoxyamine unimolecular initiators offers some advantages in comparison to the bimolecularly initiated polymerisation with improved control over polydispersity.

Subsequent to early work in nitroxide mediated controlled radical polymerisation a number of studies have further examined the mechanism and kinetics of this process. It was observed[140] that the kinetics of styrene polymerisation display an anomalous zero order in initiating alkoxyamine adduct concentration. Analysis[141] of the polymerisation kinetics resulted in the derivation of equations describing polymerisations in which the concentrations of propagating and mediating radicals reach a steady state with the loss of propagating radicals through termination balanced by the formation of fresh propagating radicals through autoinitiation. The resulting polymerisation rate is determined by the rate of propagating radical formation from styrene autopolymerisation. The derivation of this kinetic scheme suggested that only those monomers which autoinitiate thermally, as occurs in styrene[142], might be polymerised by nitroxide mediated polymerisation.

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[139] Hawker, C.J., Barclay, G.G., Orellana, A., Dao, J., Devonport, W., Macromolecules, **1996**, 29, 16, 5245-5254

[140] Catala, J.M., Bubel, F., Oulad Hammouch, S., Macromolecules, **1995**, 28, 8441-8443

[141] Fukuda, T., Terauchi, T., Goto, A., Ohno, K., Tsujii, Y., Miyamoto, T., Kobatake, S., Yamada, B., Macromolecules, **1996**, 29, 6393-6398

[142] Mayo, F.R., J. Am. Chem. Soc., **1968**, 90:5, 1289-1295

Kinetic analysis by Fischer *et al.*[143] of nitroxide mediated free radical polymerisation during the steady state period showed that the similarity between polymerisation rate and the rate of autoinitiation to be a consequence of the self-termination of transient radicals in the early stages of the reaction, resulting in a build up of an excess in the mediating nitroxide. In the absence of a feed of propagating radicals into the polymerisations the excess in persistent species reduces the subsequent level of self termination reactions, leading to exclusive cross coupling termed the 'persistent radical effect'. This term was coined by Finke[144] in reference to a general phenomena, described by Fischer, in systems in which transient and persistent radicals are formed at equal rates and in which, after a short period, an unusually selective cross coupling reaction dominates and has seen application in general organic synthesis. In polymerisations in which autoinitiation is absent this excess of persistent radical results in a shift in the capping equilibrium between homolysis and capping reactions greatly towards the capped chain ends resulting in a cessation of polymerisation.

Further kinetic analysis by Fischer[145] resulted in the development of equations describing the polymerisation rate under steady state conditions [Equation 26] in which polymerisation is determined by the persistent radical effect in the absence of autoinitiation.

$$\ln([M]/[M]_0) = \frac{-3}{2} k_p \left(\frac{K[I]_0}{3k_t} \right)^{1/3} t^{2/3}$$

Equation 26, reproduced from page 53

[143] Fischer, H., Macromolecules, **1997**, 30, 5666-5672

[144] Daikh, B.E., Finke, R.G., J. Am. Chem. Soc., **1992**, 114, 2938

[145] Fischer, H., Journal of Polymer Science: Part A: Polymer Chemistry, **1999**, 37, 1885-1901

This equation was shown to be applicable under the conditions [Equation 25]

$$k_d / k_c = K < [I]_0 \frac{k_c}{4k_t}$$

Equation 25, reproduced from page 52

Polymerisations close to but outwith these limits were suggested to result in either an uncontrolled living polymerisation or a low polydispersity non-living polymerisation. The kinetic features predicted by this analysis have since been observed[146] in polymerisations in which the rate is determined by the persistent radical effect rather than autoinitiation.

The effect of nitroxide structure on radical trapping[147&148] and alkoxyamine homolysis[149-152] reactions have been studied by a number of groups emphasising the importance of both steric bulk and electronic structure of the nitroxide mediating radical in determining the rate constants for alkoxyamine carbon to oxygen bond dissociation and nitroxide trapping of propagating radicals.

These studies suggest that the kinetic conditions set out by Fischer *et al.* for the applicability of the kinetic scheme determined by the persistent radical effect might

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[146] Lutz, J-F., Lacroix-Desmazes, P., Boutevin, B., Macromol. Rapid Commun., **2001**, 22, 189-193

[147] Bowry, V.W., Ingold, K.U., J. Am. Chem. Soc., **1992**, 114, 4992-4996

[148] Skene, W.G., Scaiano, J.C., Listigovers, N.A., Kazmaier, P.M., Georges, M.K., Macromolecules, **2000**, 33, 5065-5072

[149] Moad, G., Rizzardo, E., Macromolecules, **1995**, 28, 8722-8728

[150] Kazmaier, P.M., Moffat, K.A., Georges, M.K., Veregin, R.P.N., Hamer, G.K., Macromolecules, **1995**, 28, 1841-1846

[151] Marsal, P., Roche, M., Tordo, P., de Sainte Claire, P., J. Phys. Chem. A., **1999**, 103, 2899-2905

[152] Marque, S., Le Mercier, C., Tordo, P., Fischer, H., Macromolecules, **2000**, 33, 4403-4410

be satisfied through suitable design of nitroxides giving targeted rates of homolysis and radical trapping. Selection of suitable nitroxide mediating species might be hoped to allow an increase in the rate of polymerisation rate over that of systems in which the rate of polymerisation is determined by autoinitiation and allow the application of nitroxide mediated polymerisation to monomers which do not undergo autoinitiation without the addition of ancillary initiator.

A number of groups have noted an increased rate of styrene polymerisation whilst retaining macromolecular structural control through the use of sterically bulky nitroxide mediating species as alternatives to TEMPO, which might be expected to shift the equilibrium between the capping and homolysis reactions towards the uncapped chain ends. The N-*tert*-butyl-N'-[1-diethylphosphono-(2,2-dimethylpropyl)] nitroxide, DEPN [Figure 67] identified by Benoit *et al.*[153] has been shown to mediate polymerisation of styrene at a rate significantly faster than TEMPO[154].

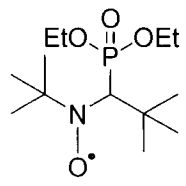

Figure 67 N-*tert*-butyl-N-[1-diethylphosphono-(2,2-dimethylpropyl)] nitroxide, DEPN, reproduced from page 60

[153] Grimaldi, S., Finet, J.P., Le Moigne, F., Zeghdaoui, A., Tordo, P., Benoit, D., Fontanille, M., Gnanou, Y., Macromolecules, **2000**, 33, 1141-1147

[154] Benoit, D., Grimaldi, S., Robin, S., Finet, J.P., Tordo, P., Gnanou, Y., J. Am. Chem. Soc., **2000**, 122, 5929-5939

Hawker *et al.*[155] showed that the use of 2,2',5-trimethyl-4-phenyl-3-azahexane-3-nitroxide, TIPNO [Figure 69] as mediating species resulted in significant acceleration in the rate of styrene polymerisation.

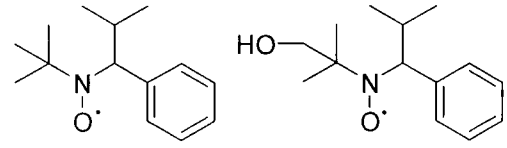

Figure 69 2,2',5 trimethyl-4-phenyl-3-azahexane-3-nitroxide, TIPNO, reproduced from page 62

Calculation of the trapping and homolysis rate constants for these bulky nitroxides have shown that these rate constants are within the limits described by Fischer for the rate of polymerisation to be determined by the persistent radical effect.

Studies on the rates of radical trapping and alkoxyamine homolysis have also shown that in addition to the effect of steric bulk there is a significant influence of solvent polarity and ability to participate in hydrogen bonding. The rates of homolysis have been shown to increase and rate of radical trapping shown to decrease with increasing solvent polarity and the ability to participate in hydrogen bonding. This, it has been suggested, is a consequence of the stabilisation of the dipolar canonical form of the nitroxide [Figure 35] in which, ESR evidence suggests, spin density is increased on the nitrogen in increasingly polar solvents.

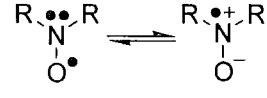

Figure 35 Nitroxide canonical forms, reproduced from page 26

[155] Benoit, D., Chaplinski, V., Braslau, R., Hawker, C.J., J. Am. Chem. Soc., **1999**, 121, 3904-3920

Substituents located adjacent to the nitroxide functionality have been shown[156] using ESR studies to have a marked influence nitroxide spin density. It is reasonable to imagine that spin density located on the nitrogen atom, and hence the reversible capping reaction may similarly be manipulated by modifying the electronic nature of adjacent substituents.

The decision was made to investigate the influence of nitroxide structure on styrene polymerisation kinetics using a series of alkoxyamines based on nitroxides derived from the pyrrolidine-N-oxyl backbone [Figure 90].

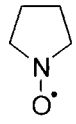

Figure 90 pyrrolidine-N-oxyl

These nitroxides were selected as suitable subjects for study as a consequence of the availability of straightforward synthetic routes to generate 2,2,5-trimethylpyrrolidin-N-oxide nitrone [Figure 91], which allow the further synthesis of a number of nitroxide structures.

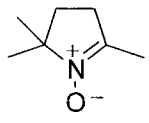

Figure 91 2,2,5-trimethylpyrrolidin-N-oxide nitrone

Similar pyrrolidine-N-oxyl nitroxide species have been previously applied as mediating species in controlled radical polymerisation; Veregin *et al.*[157]

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[156] Janzen, E.G., Haire, D.L., Chapter 6, Advances in Free Radical Chemistry, Vol 1., 253-295, **1990**, JAI Press Inc.

[157] Veregin, R.P.N., Georges, M.K., Hamer, G.K., Kazmaier, P.M., Macromolecules, 28, 13, **1995**, 4391-4398

demonstrated the use of 2,2',5,5'-tetramethyl-carboxyl pyrrolidine-N-oxyl [Figure 92] with which enhanced styrene polymerisation rate over TEMPO was observed.

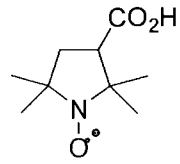

Figure 92 2, 2',5,5'-tetramethyl-3-carboxyl pyrrolidine-N-oxyl

Puts and Sogah[158] demonstrated the controlled polymerisation of styrene with enhancement in rate using the symmetrical *trans*-2,5-dimethyl-2,5-diphenylpyrrolidine-N-oxyl [Figure 63]

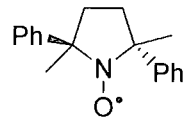

Figure 63 2,5-dimethyl-2',5'-diphenyl pyrrolidine-N-oxyl, reproduced from page 58

Polymerisations[159] of styrene have been studied utilising the sterically congested 1,1,3,3-tetraethylisoindoline-2-oxyl (TEISO) [Figure 64] based alkoxyamine in an attempt to lower the temperature necessary for polymerisation.

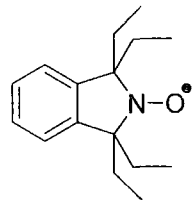

Figure 64 1,1,3,3-tetraethylisoindoline-2-oxyl (TEISO) nitroxide, reproduced from page 58

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[158] Puts, R.D., Sogah, D.Y., Macromolecules, **1996**, 29, 3323-3325

[159] Cresidio, S.P., Aldabbagh, F., Busfield, W.K., Jenkins, I.D., Thang, S.H., Zayas-Holdsworth, C., Zetterlund, P.B., Journal of Polymer Science: Part A: Polymer Chemistry, **2001**, 39, 1232-1241

Improvement[160] in rate of styrene polymerisation over TEMPO was also demonstrated in polymerisation mediated by derivatives of 2,2,5,5-tetraalkylimidazolidin-4-one-1-oxyl [Figure 64].

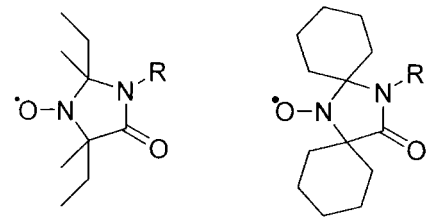


Figure 64 2,2,5,5-tetraalkylimidazolidin-4-one-1-oxyl nitroxides, reproduced from page 58

Alkoxyamines **7-10** [Figure 94], were prepared from the 2,2',5,5'-tetramethylpyrrolidine-N-oxyl (PROXYL) **1**, 2,2',5-trimethyl-5'-phenylpyrrolidine-N-oxyl **2**, 2,2',5-trimethyl-5'-N,N-dimethyl-4-aminophenylpyrrolidine-N-oxyl **3**, and 2,2',5-trimethyl-5'-(trifluoro-*p*-methyl)phenylpyrrolidine-N-oxyl **4**, nitroxides [Figure 93] through nitroxide trapping of the alkyl radical products of the addition of tert-butoxy radicals, generated at low temperature from the decomposition of DTBPO, to styrene [Figure 95]. The synthesis and characterisation of these nitroxides and associated alkoxyamines is detailed in chapter 2.

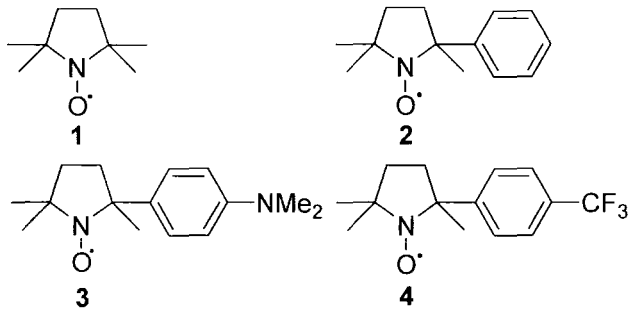


Figure 93 Nitroxides 1-4 based on pyrrolidine-N-oxyl

[160] Chong, Y.K., Ercole. F., Moad, G., Rizzardo, E., Thang, S.H., Macromolecules, 32, 21, **1999**, 6895-6903

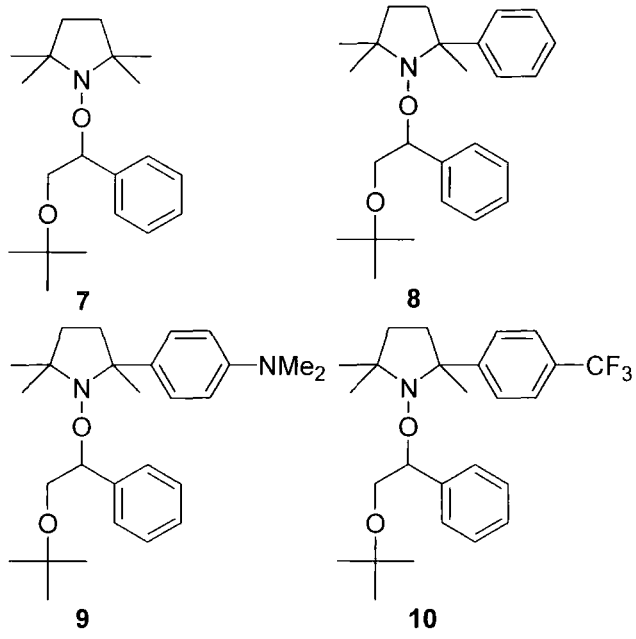


Figure 94 Alkoxyamines 7-10 utilised in styrene polymerisation

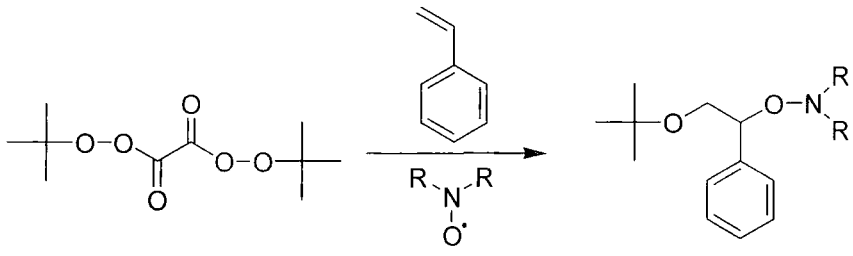
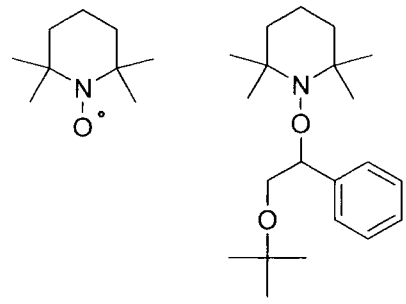


Figure 95 Di-*tert*-butyl peroxalate route to alkoxyamines

For comparison purposes a similar alkoxyamine **6** [Figure 96] was prepared by the same synthetic route from the TEMPO, 2,2,6,6-tetramethylpiperidine-N-oxyl, nitroxide **5** which has provided the basis for much of the early work in nitroxide mediated polymerisation. The synthesis and characterisation of this alkoxyamine is detailed in chapter 2.



5 6

Figure 96 TEMPO nitroxide 5 and alkoxyamine 6

The alkoxyamines **6-10** were investigated as initiators for styrene polymerisation.

Experimental

Materials and Instrumentation

Styrene was purified before use by distillation under vacuum and stored in a refrigerator, immediately prior to use any final traces of inhibitor were removed by passing the monomer through alumina. Azoisobutyronitrile, AIBN was recrystallised from methanol and stored in a refridgerator. Alkoxyamine initiators were prepared, purified and characterised as described in chapter 2.

NMR spectra were recorded in deuterated chloroform solution containing tetramethylsilane as an internal standard, using a Bruker 300MHz spectrometer. Gel permeation chromatography was performed using a Waters modular system comprising a WISP 712 autoinjector, 510 pump and either a Polymer Laboratories gel 352 column or a Linear Shodex KF80M columns at 40°C. A Waters UV440 and Waters 4100 differential refractometer were employed for detection. An injection volume of 100μl, 0.1 wt./vol % in THF at 1.0ml/min was used.

Polymerisation

Polymerisation mixtures were prepared in a two necked round bottomed flask fitted with a tap and septum. The flask was then connected to a dual vacuum and nitrogen manifold and degassed by three consecutive freeze/pump/thaw cycles and subsequently back flushed with nitrogen. The polymerisation solution was then divided equally by syringe transfer between several gas chromatography vials each fitted with septa, which had previously been flushed with nitrogen. These vials were then placed into an oil bath maintained at 125°C and sequentially removed and quench cooled in an ice bath at regular time intervals over the period of the polymerisation. Monomer conversions were calculated for each sample by collection of the ^{1}H NMR spectra and comparison of the signal integrals for the phenyl and vinyl protons.

Gel permeation chromatography for each sample was performed without any reprecipitation.

Initial experiments relied on removal of a sample from the polymerisation vessel via syringe. The samples were then weighed and monomer removed *in vacuo* and conversion calculated by weight loss although this method of calculating conversion led to a substantial variability in results.

Polymerisation solutions were made up as:

AIBN (azoisobutyronitrile) (0.205g, 0.125mmol) and styrene (10g, 96mmol)

Alkoxyamine **6-10** (0.25mmol) and styrene (10g, 96mmol).

Alkoxyamine **8,** 2,2',5-trimethyl-5'-phenylpyrrolidine-N-oxyl was also investigated at varying concentrations (0.069g, 0.18mmol; 0.053g, 0.14mmol) with styrene (10g, 96mmol)

Results and Discussion

For comparison purposes polymerisations of styrene were performed at 125°C one initiated by thermal autopolymerisation and another with azoisobutyronitrile, AIBN, a conventional free radical initiator. The polymerisation of styrene initiated by a conventional initiator such as AIBN can be seen from the plot of logarithmic conversion index with time [Figure 97] to reach approximately 50% conversion over the period of an hour at 125°C.

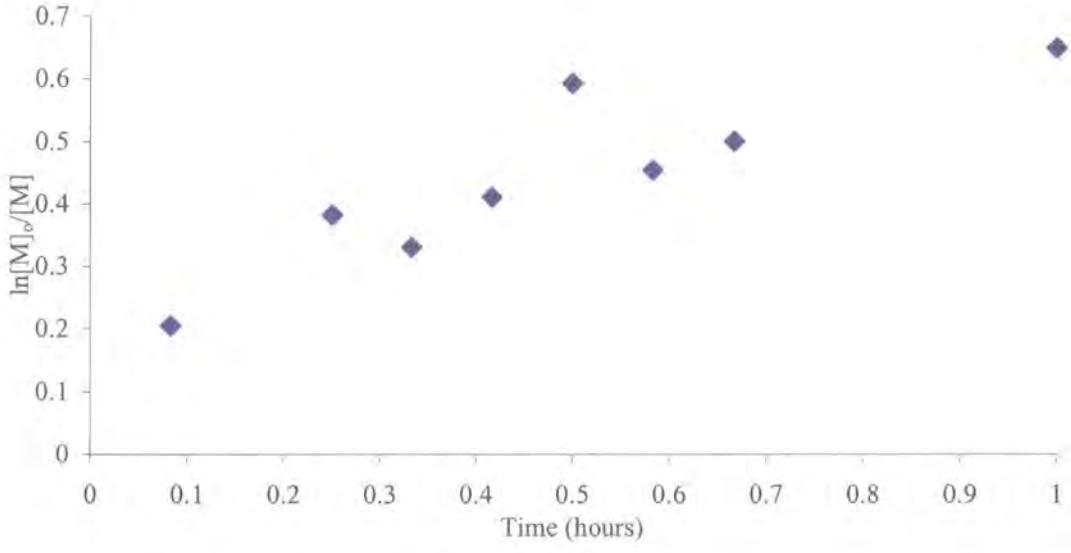


Figure 97 AIBN initiated polymerisation of styrene

Autopolymerisation of styrene in the absence of initiator can be seen from the plot of logarithmic conversion index [Figure 98] with time be somewhat slower reaching 50% conversion after 3 hours at 125°C.

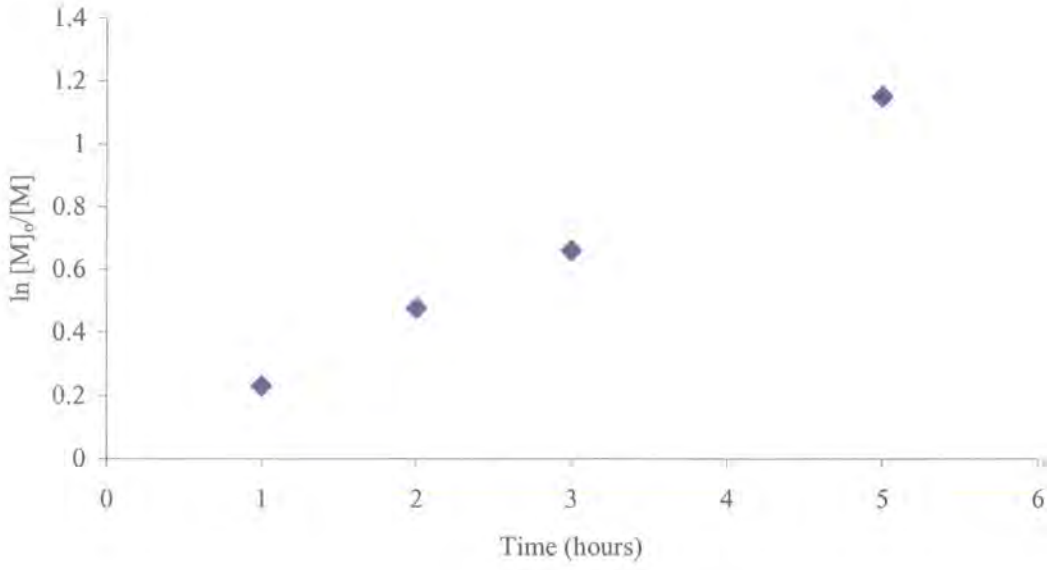


Figure 98 Thermal autopolymerisation of styrene at 125°C

Previous work[161] has investigated the polymerisation of styrene mediated by nitroxides **1-4** in with in-situ generation of initiating alkoxyamine.

In this study alkoxyamines were formed by the gentle heating of a styrene solution of the appropriate nitroxide (0.023mol L^{-1}) and di-*tert*-butyl peroxalate (0.11mol L^{-1}) to 40°C for one hour. Subsequent to this polymerisation was initiated by heating of the resulting mixture to 125°C.

It was observed within this prior work that polymerisation mediated by nitroxide **1** was a middle case with polymerisation mediated by nitroxide **3** significantly slower with a long induction period after which conversion begins to increase. Polymerisations mediated by nitroxides **2** and **4** were somewhat faster. Polymerisations mediated by all nitroxides **1-4** were shown to have a linear increase

[161] Cameron, N.R., Reid, A.J., Span, P., Bon, S.A.F., van Es, J.J.G.S., German, A.L., Macromol. Chem. Phys., **2000**, 201, 2510-2518

in molecular weight with conversion with product polydispersities in the range of 1.64 to 1.16.

The observation of an induction period in the polymerisation mediated by nitroxide **3** may be explained taking into consideration subsequent results described in chapter 2 in the synthesis of the analogous alkoxyamine **9** for which a very poor yield was obtained. N,N'-dimethylaniline has been previously described as participating in a redox reaction with benzoyl peroxide [Figure 99]. The product of this reaction can thermally dissociate to generate a benzyloxy radical and an amine radical cation. The amine radical cations formed have also been proposed to potentially undergo the loss of a proton to form an anilinomethyl radical resulting in generation of a number of potential side products.

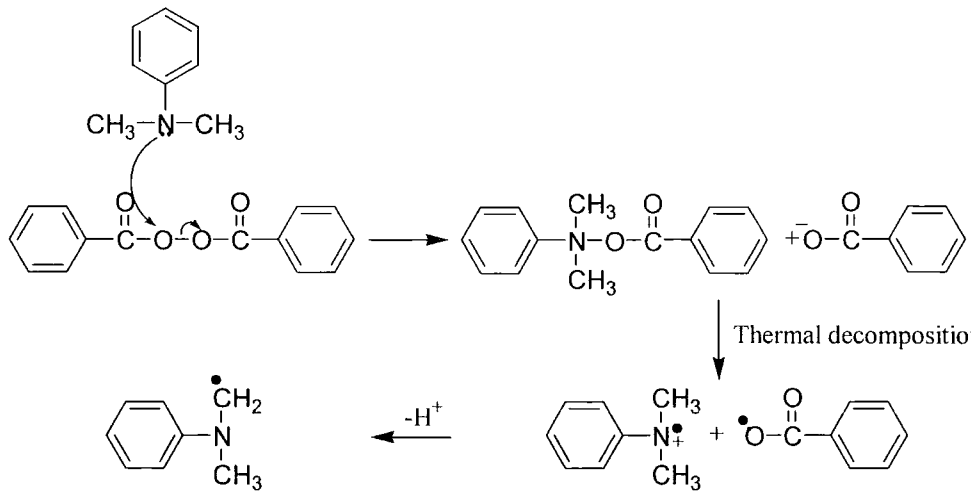


Figure 99 Redox reaction of benzoyl peroxide with tertiary amine

It is reasonable to suggest that a similar reaction might occur between the amino group of nitroxide **3** and DTBPO in both synthesis and in-situ generation of alkoxyamine, which would explain the poor alkoxyamine yield in synthesis. With in-situ formation of alkoxyamines this might be expected to occur in similarly poor yield with the formation of numerous side products accounting for the observation of an induction period in polymerisation.

Although nitroxides **1-4** are chiral species and will couple with prochiral benzylic radicals [Figure 100] to produce diastereomeric alkoxyamines [Figure 101] as detectable by proton NMR, no effort was made to resolve these species after synthesis.

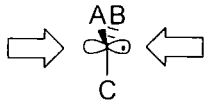


Figure 100 Prochiral faces of carbon centred radical

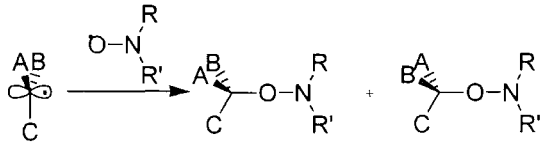


Figure 101 Coupling of prochiral radical with nitroxide

Although it has been proposed that diastereomeric alkoxyamines have the potential to have different alkoxyamine carbon to oxygen bond strengths as a consequence of differences in steric strain it was decided that the effect of any diastereoisomerism in initiating alkoxyamine adduct would be insignificant in polymerisation beyond the initial homolysis step. Upon heating to polymerisation temperature the homolysis and capping reactions would quickly result in re-estabishment of the equilibrium proportions of the propagating polymer terminus alkoxyamine stereochemistries. Studies by Braslau *et al.*[162] into the coupling of chiral nitroxides with prochiral radicals as a potential means of chiral induction noted no significant selectivity further suggesting that differences in alkoxyamine bond homolysis energy are small enough to be considered insignificant.

[162] Braslau, R., Burrill, L.C., Mahal, L.K., Wedeking, T., Angew. Chem. Int. Ed. Engl., **1997**, 36, 3, 237-238

The isolated alkoxyamines **6-10** were utilised in the initiation of styrene polymerisation at 125°C. From the plot of logarithmic conversion index against time [Figure 102] it can be seen that the alkoxyamines used can be divided into two groups. Those polymerisations initiated by TEMPO based alkoxyamine **6** and alkoxyamines **7** & **9** produced similar rates of polymerisation which are slightly slower than the rate observed for autoinitiation of styrene while the use of alkoxyamines **8** & **10** gave significantly faster rates approximately equivalent to the rate of polymerisation through autoinitiaion of styrene.

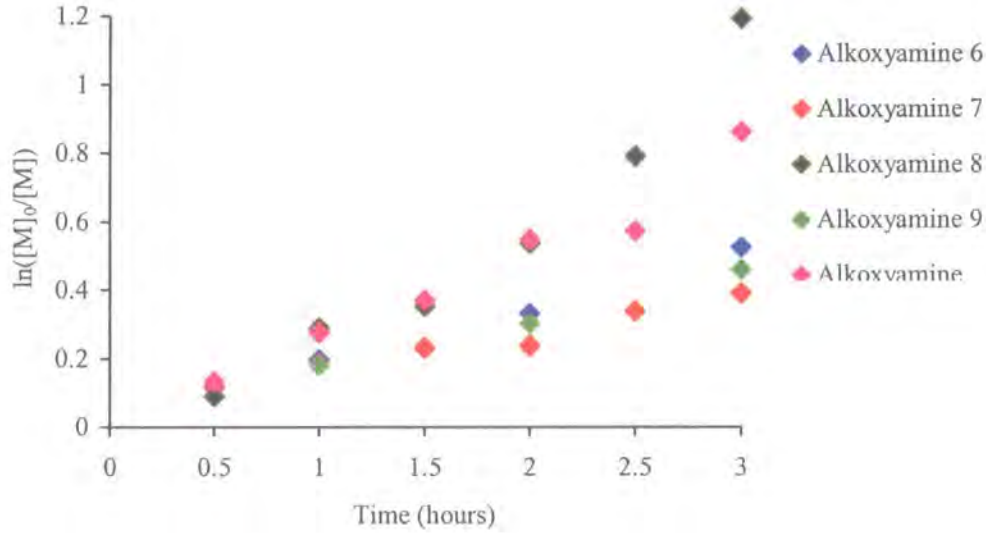


Figure 102 Log conversion against time for alkoxyamine initiated polymerisation of styrene

Alkoxyamine	Initial slope	k_{obs} ($Lmol^{-1}s^{-1}$)
6	4.76×10^{-5}	0.0021
7	3.58×10^{-5}	0.0016
8	7.43×10^{-5}	0.0032

9	4.16×10^{-5}	0.0018
10	7.61×10^{-5}	0.0032

Plotting number average molecular weight against conversion [Figure 103] and polydispersity against time [Figure 104] as obtained by gel permeation chromatography, it can be seen that the polymerisations initiated by all the alkoxyamines **6-10** under study result in a linear increase in number average molecular weight with conversion and polydispersity indices which reduce to approximately 1.25-1.5 over the timescale of polymerisation. The results of gel permation chromatography would appear to be indicative of a controlled and living polymerisation process although in the polymerisation initiated by alkoxyamine **10** a large deviation from theoretical molecular weight growth and a higher polydispersity index are observed. This would appear to indicate a reduction in control over the polymerisation process. Some explaination for this could come from the synthesis of this alkoxyamine based on nitroxide **4** described in Chapter 2 which can be seen to result in a yield approximately half that obtained for the synthesis of alkoxyamines derived from TEMPO or nitroxides **1** and **2** which might suggest a poorer efficiency of radical trapping by nitroxide.

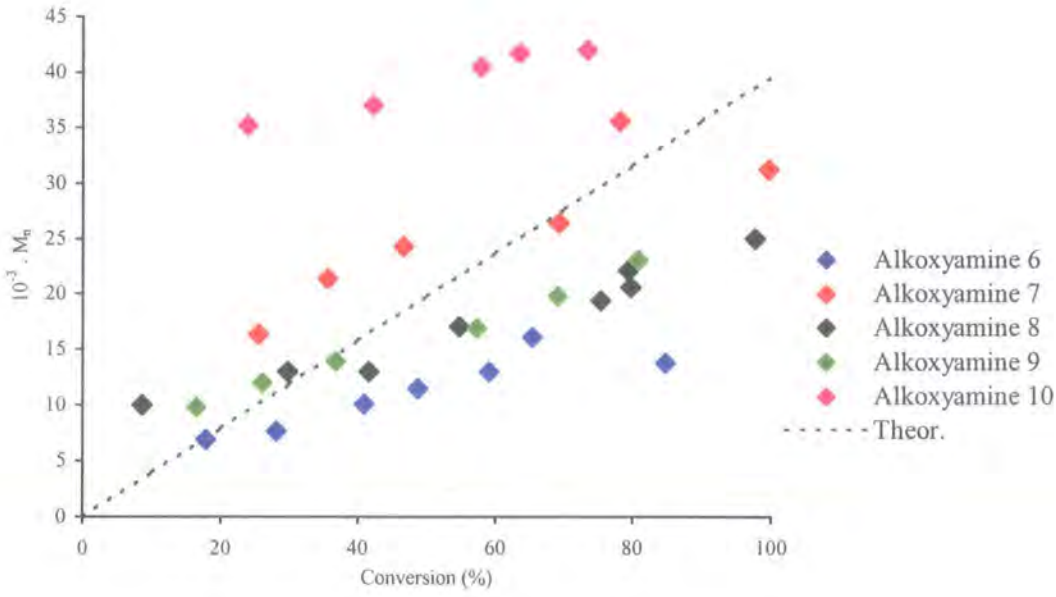


Figure 103 Number average molecular weight against conversion for alkoxyamine initiated polymerisation of styrene

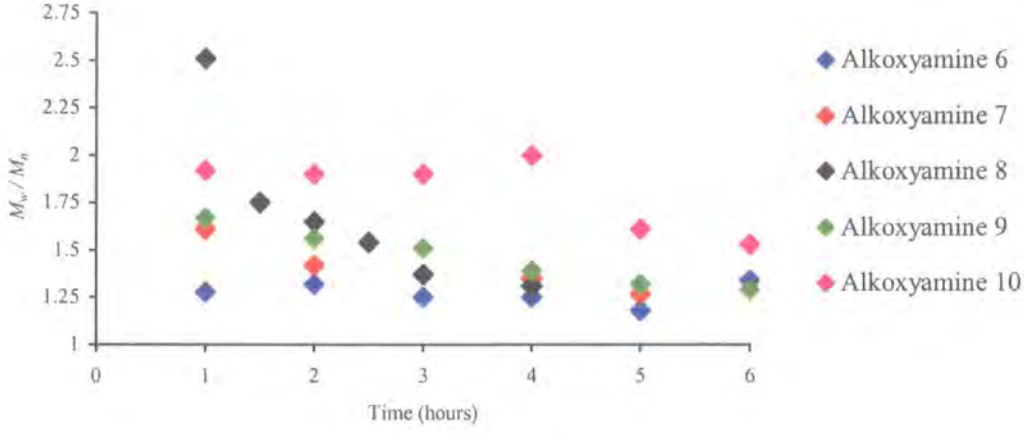


Figure 104 Polydispersity index vs. time for alkoxyamine initiated polymerisation of styrene

It is worth noting that while the study examining polymerisation with in-situ generation of alkoxyamine from nitroxide **3** resulted in observation of an induction period prior to the beginning of polymerisation and subsequent rate of styrene polymerisation slower than that mediated by TEMPO. The rate of polymerisation initiated by alkoxyamine **9** is comparable to that initiated by alkoxyamine **7** and

TEMPO alkoxyamine **6.** This would suggest that the redox side reactions discussed previously are indeed a significant complicating factor in the comparison of activity of nitroxides **1-4** in mediating polymerisation with in-situ generation of alkoxyamines.

Polymerisation rates observed with alkoxyamines **8** and **10** were approximately the same as the rate of thermal autopolymerisation of styrene while alkoxyamines **6,7** and **9** were somewhat slower.

Comparison of the structures of mediating nitroxides in these polymerisations would suggest that there is a significant influence of nitroxide electronic structure on polymerisation. Use of alkoxyamine **8** which generates the mediating nitroxide **2** bearing a phenyl substituent results in a faster rate of polymerisation than that initiated by alkoxyamine **7** generating mediating nitroxide **1** probably as a result of increase in nitroxide steric bulk. Comparing polymerisations initiated by alkoxyamines **8** and **9** which generate mediating nitroxides **2** and **3** we see a reduced polymerisation rate with initiation by alkoxyamine **9** which bears an electron donating group. This would suggest that this change in mediating nitroxide results in a lower concentration of propagating radicals during the steady state period of polymerisation. Comparison of polymerisations initiated by alkoxyamines **8** and **10** which generate mediating nitroxides **2** and nitroxide **4** with an electron withdrawing substituent results in observation of a reduction in polymerisation control with alkoxyamine **10** although with no increase in polymerisation rate.

In order to further investigate the polymerisation of styrene initiated by alkoxyamine **8** further polymerisations were carried out utilising this species at differing concentrations. This study was carried out in order to determine which kinetic scheme best describes styrene polymerisation initiated by this species.

Polymerisations determined by the rate of monomer autoinitiation result in observation of a zero order dependence of polyerisation rate in initiating adduct while those determined by the persistent radical effect, whose kinetic scheme has been described by Fischer, are predicted to display a 1/3 order polymerisation rate dependence in initiating alkoxyamine concentration. Polymerisations initiated by 0.18mmol and 0.14mmol alkoxyamine in 10g styrene can be seen from the logarithmic conversion index with time [Figure 105] to proceed at similar rates. Calculating fits to these polymerisation results in observed rates identical to that observed in a polymerisation initiated by 0.23mmol alkoxyamine in 10g styrene showing that polymerisation rate is determined by autoinitiation. Further experiments over a wider range of concentrations showed similar behaviour.

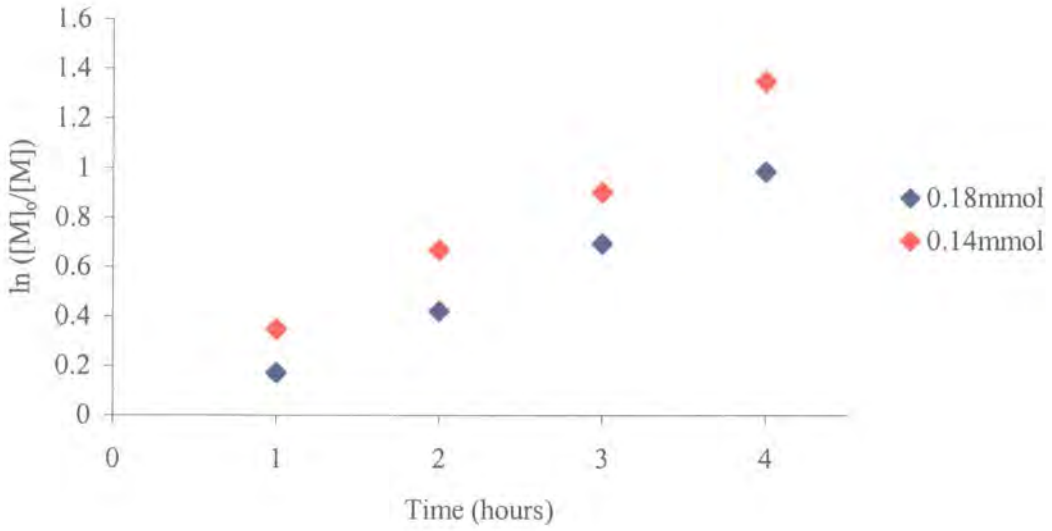


Figure 105 Polymerisation of styrene at 125°C initiated by 0.14mmol and 0.18mmol alkoxyamine 8

Summary

Studies into the effectiveness of alkoxyamines based on pyrrolidine-N-oxyl nitroxide in initiating styrene polymerisation shows an influence of nitroxide electronic

structure on polymerisation rate and macromolecular control analogous to the influence of solvent polarity observed by other researchers. Alkoxyamine **8** which generates nitroxide **2** as a mediating species was observed to result in an improved polymerisation rate over TEMPO based alkoxyamine while retaining control over product polydispersity. This rate of polymerisation initiated by this alkoxyamine was however shown to be determined by the autoinitiation rate of styrene.

Chapter 4 - *n*-Butyl Acrylate Polymerisation

Introduction

Although the intitial patent from Rizzardo *et al.*[163] covering nitroxide mediated living radical polymerisation evinced the synthesis of acrylate and methacrylate oligomers, the majority of the studies subsequent to the first practical demonstrations of the reversible nitroxide capping of growing polymer chains by Georges[164] and later Hawker[165] have investigated the polymerisation of styrene and related monomers. The application of TEMPO and similar nitroxides to the polymerisation of monomers such as acrylates and methacrylates has been restricted as a consequence of the small equilibrium constant between capping and homolysis reaction and the absence of autoinitiation as an additional radical source to counter the loss of propagating chains through bimolecular termination. In the polymerisation of styrene, a feed of new propagating radicals is maintained through thermal autoinitiation[166] and it is this radical source that results in propagation over a reasonable timescale. This dependence on autoinitiation as a radical source leads to the observation of unusual polymerisation rate kinetics.

In styrene polymerisation initiated by a unimolecular di-*tert*-butyl nitroxide adduct, the polymerisation rate has been shown[167] to be independent of the concentration of

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[163] Solomon, D.H., Rizzardo, E., Caclioli, P., EP0135280

[164] Georges, M.K., Veregin, R.P.N., Kazmaier, P.M., Hamer, G.K., Macromolecules, **1993**, 26, 2987-2988

[165] Hawker, C.J., J. Am. Chem. Soc., **1994**, 116, 11185-11186

[166] Mayo, F.R., J. Am. Chem. Soc., 90:5, **1968**

[167] Catala, J.M., Bubel, F., Oulad Hammouch, S., Macromolecules, **1995**, 28, 8441-8443

the alkoxyamine initiator and is determined by the rate of thermal autopolymerisation of styrene at the same temperature[168]. The conclusion was drawn that thermal autoinitiation was responsible for supplying the majority of propagating radicals and that in the absence of autoinitiation the lack of a source of new radicals prevents the homopolymerisation of acrylate and methacrylate monomers.

In controlled radical polymerisation self termination of transient radicals in the early stages of the reaction results in a build up of an excess of the persistent species. This excess in persistent species leads to an exclusive cross coupling. This is a general phenomenon observed in systems in which transient and persistent radicals are formed at equal rates and in which, after a short period, this selective cross coupling reaction dominates termed the persistent radical effect.

Subsequently analytical expressions were derived by Fischer *et al.*[169] describing the kinetics applicable in which the rate of polymerisation [Equation 26] is determined by the persistent radical effect in the absence of autoinitiation under steady state conditions.

$$\ln([M]/[M]_0) = -\frac{3}{2}k_p\left(\frac{K[I]_0}{3k_t}\right)^{1/3} t^{2/3}$$

Equation 26, reproduced from page 53

This equation was shown[170] to apply within certain limitations for equilibrium between homolysis and capping reactions for a given propagation rate conditions [Equation 25].

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[168] Geszta, D., Matyjaszewski, K., Macromolecules, **1996**, 29, 5239-5240

[169] Fischer, H., Macromolecules, **1997**, 30, 5666-5672

[170] Fischer, H., Journal of Polymer Science: Part A: Polymer Chemistry, **1999**, 37, 1885-1901

$$k_d / k_c = K < [I]_0 \frac{k_c}{4k_t}$$

Equation 25, reproduced from page 52

The derivation of this kinetic scheme suggests that polymerisation of monomers in which autoinitation is absent is possible through selection of suitable nitroxides with rate constants for capping and homolysis reactions within these limits. Polymerisation of monomers which do not meet these conditions were predicted to result in a polymerisation too slow to be of practical application. Systems close to but outwith the ideal conditions were suggested[171] to result either in an uncontrolled living or a controlled non-living polymerisation.

The controlled copolymerisation of methyl methacrylate or butyl acrylate monomers with styrene has been demonstrated Hawker *et al.*[172] utilising a unimolecular initiator based on TEMPO. The extent of macromolecular control was shown to vary with the styrene content and a rise in polydispersity index was observed with reducing styrene fraction. Georges studied[173] the homopolymerisation of *n*-butyl acrylate via bimolecular initiation with 4-oxo-TEMPO in conjunction with AIBN at 150°C over nine hours. An increase in molecular weight with conversion was observed although an increasing polydispersity index with time was also noted, indicating poor control over macromolecular architecture. Block copolymers were also prepared from both 4-oxo-TEMPO terminated polystyrene with *n*-butyl acrylate and 4-oxo-TEMPO

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[171] Souaille, M., Fischer, H., Macromolecules, **2000**, 33, 7378-7394

[172] Hawker, C.J., Elce, E., Dao, J., Volksen, W., Russell, T.P., Barclay, G.G., Macromolecules, **1996**, 29, 2686-2688

[173] Listigovers, N.A., Georges, M.K., Odell, P.G., Keoshkerian, B., Macromolecules, **1996**, 29, 8992-8993

terminated poly(*n*-butylacrylate) with styrene demonstrating the living nature of the resulting product.

The effects of nitroxide structure on the trapping[174&175] of carbon centred radicals and alkoxyamine homolysis[176-178] have been examined by a number of groups which showed a significant effect of structure on both reactions.

As a result of studies showing a decrease in trapping rate and increase in homolysis rate with increased steric bulk in mediating nitroxide resulting in a shift of the capping equilibrium more towards the uncapped chain ends, Fukuda[179] investigated the use of di-*tert*-butyl nitroxide as a potential mediating species for the polymerisation of acrylates and methacrylates at 120°C. An increase in molecular weight with time was observed although the rate of conversion was seen to slow significantly after approximately six hours and 30% conversion. Addition of a small amount dicumyl peroxide to provide a feed of propagating radicals resulted in an increase in both polymerisation rate and final conversion. The polydispersity index of samples taken over polymerisation were shown to pass through a minimum before then rising with increasing conversion. This anomalous behaviour in polydispersity index was ascribed to the formation of dead polymers chains by hydrogen transfer

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[174] Bowry, V.W., Ingold, K.U., J. Am. Chem. Soc., **1992**, 114, 4992-4996

[175] Skene, W.G., Scaiano, J.C., Listigovers, P.M., Georges, M.K., Macromolecules, **2000**, 33, 5056-5072

[176] Moad, G., Rizzardo, E., Macromolecules, **1995**, 28, 87

[177] Kazmaier, P.M., Moffat, K.A., Georges, M.K., Veregin, R.P.N., Hamer, G.K., Macromolecules, **1995**, 28, 1841-1846

[178] Marsal, P., Roche, M., Tordo, P., de Sainte Claire, P., J. Phys. Chem., A., **1999**, 103, 2899-2905

[179] Goto, A., Fukuda, T., Macromolecules, **1999**, 32, 618-623

disproportionation to form alkene terminated chain ends and hydroxylamine. The polymerisation of acrylates is prone to transfer to polymer through abstraction of hydrogen, and it was suggested by analogy that acrylate hydrogens are particularly labile to this termination process.

Charleux *et al.*[180] demonstrated the synthesis of homo and block copolymers of *n*-butyl acrylate through polymerisation initiated with either styryl-TEMPO or polystyryl-TEMPO alkoxyamine adducts. These polymerisations mediated by TEMPO nitroxide were however shown to cease at low levels of conversion. Analysis of the polymeric products by proton NMR and MALDI-TOF spectroscopy indicated that the chain ends were almost exclusively unsaturated and are therefore likely to be a product of hydrogen transfer disproportionation rather than the TEMPO capped alkoxyamine species.

Recent developments in application of novel nitroxides which have been shown in styrene polymerisation to fit the capping homolysis equilibrium steady state conditions set out by Fischer *et al.* and developed independently by Fukuda; the rates of styrene polymerisation were shown to be no longer determined by autopolymerisation with a zero rate order in the initiating species. These new nitroxides have been furthermore shown to extend the range of monomers available to nitroxide mediated radical polymerisation.

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[180] Burguière, C., Dourges, M.A., Charleux, B., Vairon, J.P., Macromolecules, **1999**, 32, 3883-3890

N-*tert*-butyl-N-[1-diethylphosphono-(2,2'-dimethylpropyl)] nitroxide, DEPN[181] [Figure 67] has been shown to result in a controlled polymerisation of *n*-butyl acrylate to give a low polydispersity product[182&183].

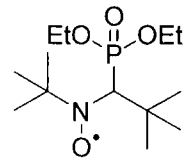

Figure 67 N-*tert*-butyl-N-[1-diethylphosphono-(2,2-dimethyl propyl)] nitroxide, DEPN, reproduced from page 60

Hawker *et al.* [184] identified 2,2',5-trimethyl-4-phenyl-3-azahexane-3-nitroxide, TIPNO [Figure 68], through screening of several nitroxides. When used as the styryl alkoxyamine adduct to initiate the polymerisation of *n*-butyl acrylate, this resulted in a polymer product with a polydispersity of 1.44. The rate of polymerisation was shown to be controllable by the addition of a small amount of acetic anhydride (acceleration) or excess nitroxide (retardation) with polydispersity index related to the rate of polymerisation.

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[181] Grimaldi, S., Finet, J.P., Le Moigne, F., Zeghdaoui, A., Tordo, P., Benoit, D., Fontanille, M., Gnanou, Y., Macromolecules, **2000**, 33, 1141-1147

[182] Benoit, D., Grimaldi, S., Robin, S., Finet, J.P., Tordo, P., Gananou, Y., J. Am. Chem. Soc., **2000**, 122, 5929-5939

[183] Lacroi-Desmazes, P., Lutz, J.F., Chauvin, F., Severac, R., Boutevin, B., Macromolecules, **2001**, 34, 8866-8871

[184] Benoit, D., Chaplinski, V., Braslau, R., Hawker, C.J., J. Am. Chem. Soc., **1999**, 121, 3904-3920

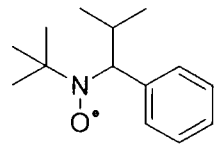

Figure 68 2,2',5-trimethyl-4-phenyl-3-azahexane-3-nitroxide, TIPNO, reproduced from page 62

This TIPNO nitroxide was used to prepare random copolymers of butyl acrylate or methyl methacrylate with styrene with greater polydispersity control than that previously observed for similar copolymer prepared with the TEMPO mediating nitroxide, even up to high acrylate content. Use of this nitroxide in the mediation of controlled radical polymerisation resulted in the absence of any detectable chain end unsaturation formed through hydrogen transfer disproportionation decomposition, as was noted in previous attempts to mediate this polymerisation with TEMPO[185].

Hydrogen transfer disproportionation of alkoxyamine chain ends resulting in the formation of dead polymer has been shown[186] to be reduced in polymerisations utilising bulky nitroxides.

Investigation of the utility in styrene polymerisation of a number of alkoxyamines based on the five membered pyrrolidine-N-oxyl backbone has shown that polymerisations initated by 2-*tert*-butoxy-1-phenyl-1-(1-oxy-2,5,5-trimethyl-2-phenyl-pyrrolidinyl)ethane, alkoxamine **8** were notably faster than comparable polymerisations initiated by 2-*tert*-butoxy-1-phenyl-1-(1-oxy-2,2,6,6-tetramethylpiperidinyl)ethane, alkoxyamine **6** based on the TEMPO nitroxide which has formed the basis for many investigations into nitroxide mediated controlled

[185] Rodlert, M., Harth, E., Rees, I., Hawker, C.J., Journal of Polymer Chemistry, **2000,** 38, 4749-4763

[186] Goto, A., Kwak, Y., Yoshikawa, C., Tsujii, Y., Sugiura, Y., Fukuda, T., Macromolecules, **2002**, 35, 3520-3525

radical polymerisation. It was decided to investigate and compare further the utility of these alkoxyamines in polymerisation of n-butyl acrylate.

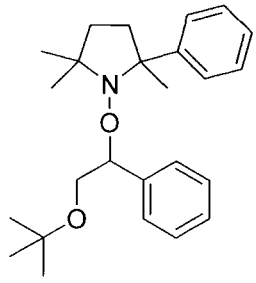

Figure 106 2-*tert*-butoxy-1-phenyl-1-(1-oxy-2,5,5-trimethyl-2-phenyl-pyrrolidinyl)ethane alkoxyamine 8

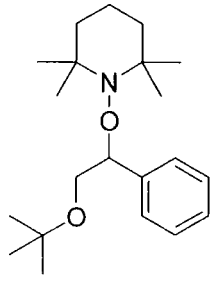

Figure 107 2-*tert*-butoxy-1-phenyl-1-(1-oxy-2,2,6,6-tetramethylpiperidinyl)ethane alkoxyamine 6

Experimental

Polymerisation mixtures were prepared in a two-necked round bottomed flask to which a tap and septum were fitted. The flask was then connected to a vacuum/nitrogen manifold and degassed by three consecutive freeze/pump/thaw cycles before being back flushed with nitrogen. In order to avoid any potential difficulties in removing increasingly viscous samples from bulk polymerisation the solution was then divided approximately equally by syringe transfer between several gas chromatography vials fitted with septa, which had previously been flushed with nitrogen. Polymerisation was initiated by immersion of the vials in an oil bath maintained at 125°C. Over the duration of polymerisation vials were sequentially

removed and quench cooled in an ice bath. Conversion was then calculated for each sample by collection of the ^{1}H NMR spectra and comparison of the signal integrals. Gel permeation chromatography was performed on each sample without any precipitation step.

The following polymerisation solutions were prepared:

AIBN (azoisobutyronitrile) (0.125mmol) and *n*-butyl acrylate (10g, 78mmol)

Alkoxyamine **6** (0.125mmol) and *n*-butyl acrylate (5.0g, 39mmol)

Alkoxyamine **8** (0.125mmol) and *n*-butyl acrylate (5.0g, 39mmol)

Alkoxyamine **8** (0.01mmol), *n*-butyl acrylate (2.5g, 20mmol) and a *n*-butyl acrylate/nitroxide **2** solution (2.5g, 20mmol containing 0.001mmol nitroxide **2**)

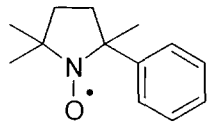

Figure 108 2,5,5-trimethyl-2-phenylpyrrolidine-N-oxyl nitroxide 2

This was repeated with *n*-butyl acrylate (3.5g, 27mmol) and *n*-butyl acrylate/nitroxide **2** stock solution (1.5g, 12mmol containing 0.0006mmol nitroxide **2**), *n*-butyl acrylate (4g, 31mmol) and *n*-butyl acrylate/nitroxide **2** stock (1g, 8mmol containing 0.0004mmol nitroxide **2**), *n*-butyl acrylate (4.5g, 35mmol) and *n*-butyl acrylate/nitroxide **2** stock (0.5g, 4mmol containing 0.0002mmol nitroxide **2**)

Poly(*n*-butyl acrylate) (5g prepared from 0.0476g, 1.25mmol, 2,2',5-trimethyl-5'-phenyl pyrrolidine-N-oxyl and 5g *n*-butyl acrylate) and styrene (5g, 48mmol)

Materials and instrumentation

n-Butyl acrylate and styrene were purified prior to use by distillation under nitrogen and passed through a column of alumina to remove any traces of inhibitor. Alkoxyamines and nitroxide were synthesised and purified as described in chapter 2.

NMR spectra were recorded in deuterated chloroform solution containing tetramethyl silane as an internal standard, using a Bruker 300MHz spectrometer. Gel permeation chromatography was performed using a Waters modular system comprising a WISP 712 autoinjector, 510 pump and either a Polymer Laboratories gel 352 column or a Linear Shodex KF80M columns at 40°C. A Waters UV440 and Waters 4100 differential refractometer were employed for detection. An injection volume of 100μl, 0.1 wt./vol % in THF at 1.0ml/min was used.

Results and Discussion

The polymerisation of *n*-butyl acrylate initiated by azoisobutyronitrile can be seen from the plot of logarithmic conversion index against time [Figure 109] to reach nearly 80% conversion in less than 5 minutes after which a slow increase in conversion is observed. This is as might be expected due to the rapid breakdown of AIBN at 125°C and the large propagation rate constant of *n*-butyl acrylate.

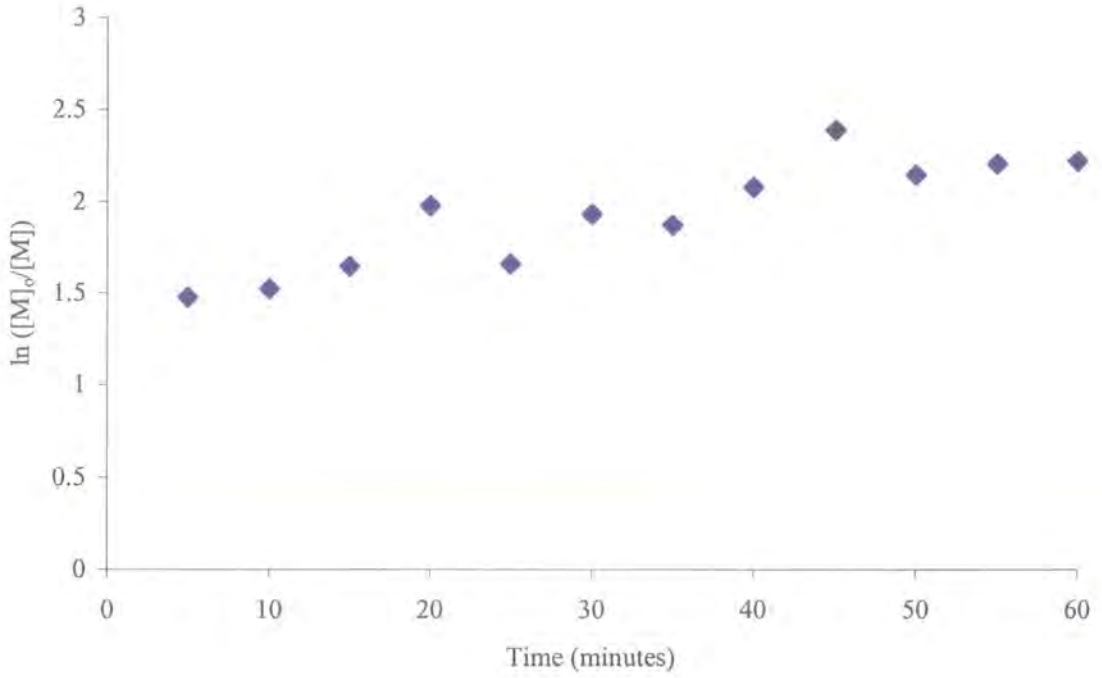

Figure 109 Butyl acrylate polymerisation at 125°C initiated by AIBN

Heating of *n*-butyl acrylate at 125°C in the absence of initiator can be seen from the plot of logarithmic conversion index against time [Figure 110] to result in a slow polymerisation reaching 32% conversion after five minutes and increasing to reach 90% after 45 minutes. This is despite the repeated assertions in the literature that no autoinitiation occurs with this monomer, the polymerisation presumably being initiated by very small levels of impurities. Subsequent investigations using both NMR and headspace GPC analysis of aerated and degassed samples did not lead to identification of those species responsible for initiation of this polymerisation.

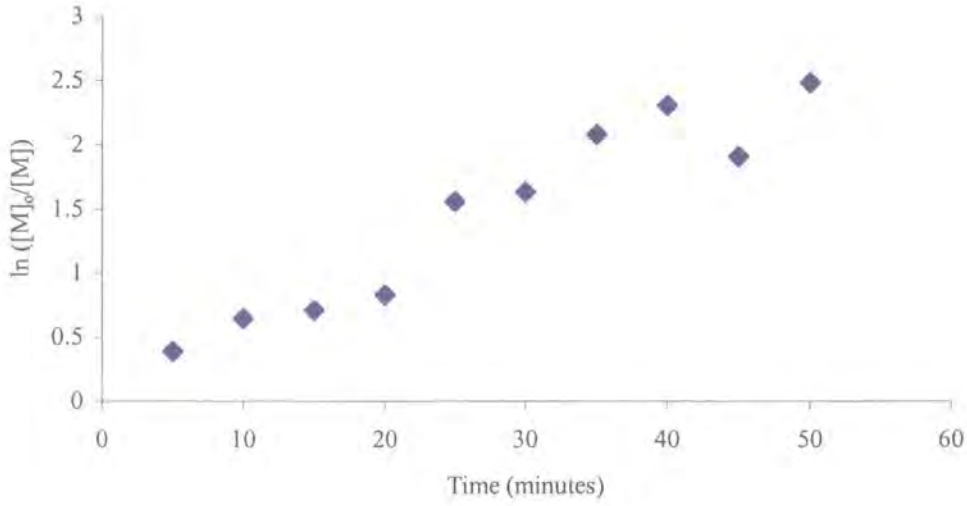

Figure 110 Butyl acrylate thermal autoinitiation at 125°C

Alkoxyamine **6** based on the TEMPO nitroxide was investigated in the polymerisation of *n*-butyl acrylate. Samples from this polymerisation showed very low conversion even after heating at 125°C for up to twelve hours reaching only 10% conversion after this time [Figure 111].

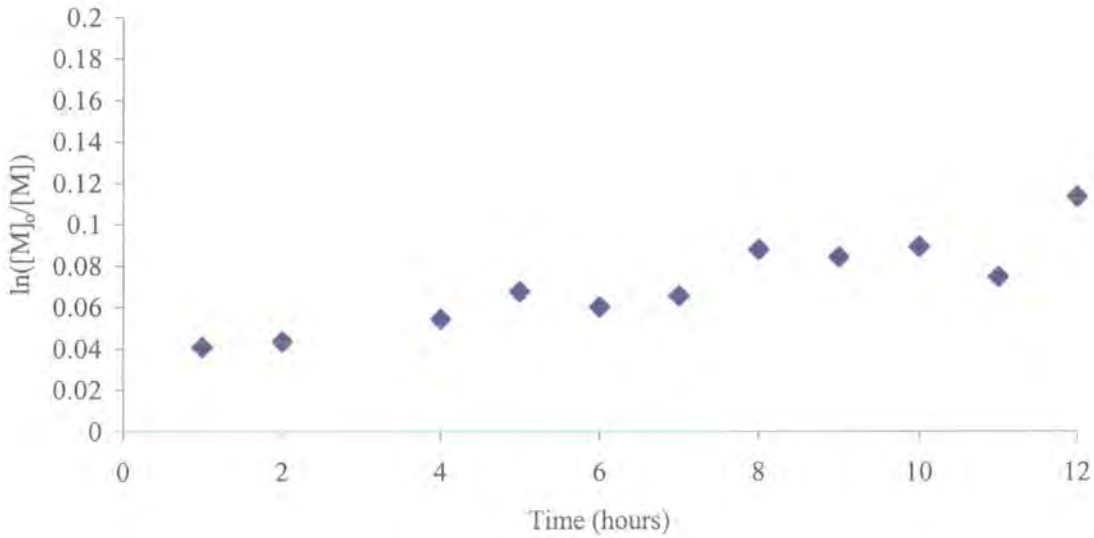

Figure 111 TEMPO alkoxyamine intiated polymerisation of *n*-butyl acrylate at 125°C

Polymerisation of *n*-butyl acrylate at 125°C initiated by alkoxyamine **8** can be seen from the plot of logarithmic conversion index [Figure 112] to reach 67% conversion within the five minutes prior to the removal of the first sample with a subsequent increase in conversion to 85% over the next hour.

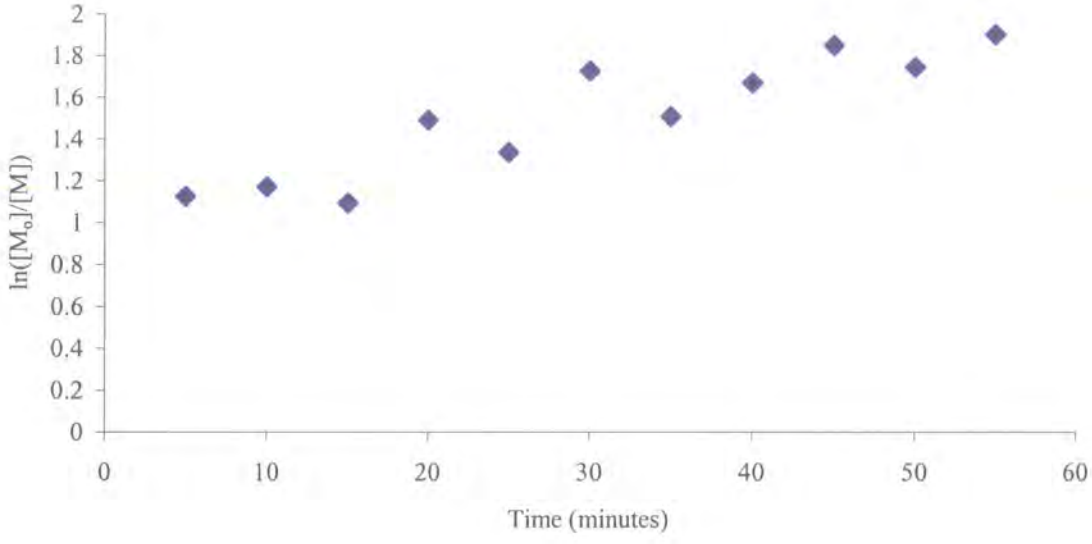

Figure 112 Alkoxyamine 8 initiated polymerisation of *n*-butyl acrylate at 125°C

Gel permeation chromatography of samples from this polymerisation [Figure 113] show that number average molecular weight does not increase with time as might be expected from a controlled radical polymerisation. The product polydispersity is broad throughout polymerisation without reducing with conversion which again is atypical of a controlled radical polymerisation.

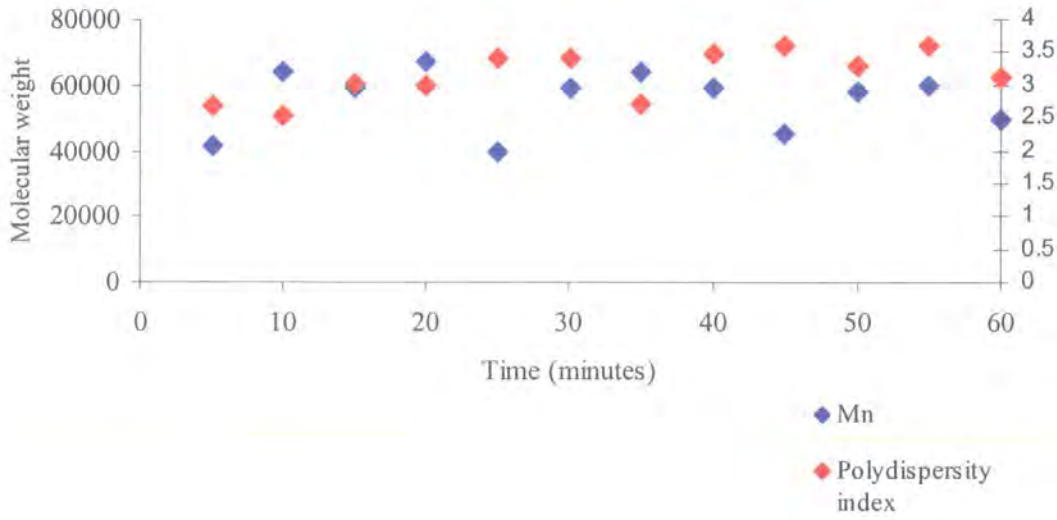

Figure 113 Molecular weight data for *n*-butyl acrylate polymerisation at 125°C initiated by alkoxyamine 8

Addition of small quantities of free nitroxide have been shown by other workers to result in a reduction in polymerisation rate and an improvement in control over macromolecular architecture. Studies were subsequently carried out with added nitroxide **2** molar concentrations of 2%, 5% and 10% relative to alkoxyamine **8**. The plots of logarithmic conversion index with time show the presence of an induction period which is dependent on the level of excess nitroxide this is approximately forty minutes for 10% excess [Figure 114] and twenty minutes for 2% [Figure 115] excess after which polymerisation proceeds.

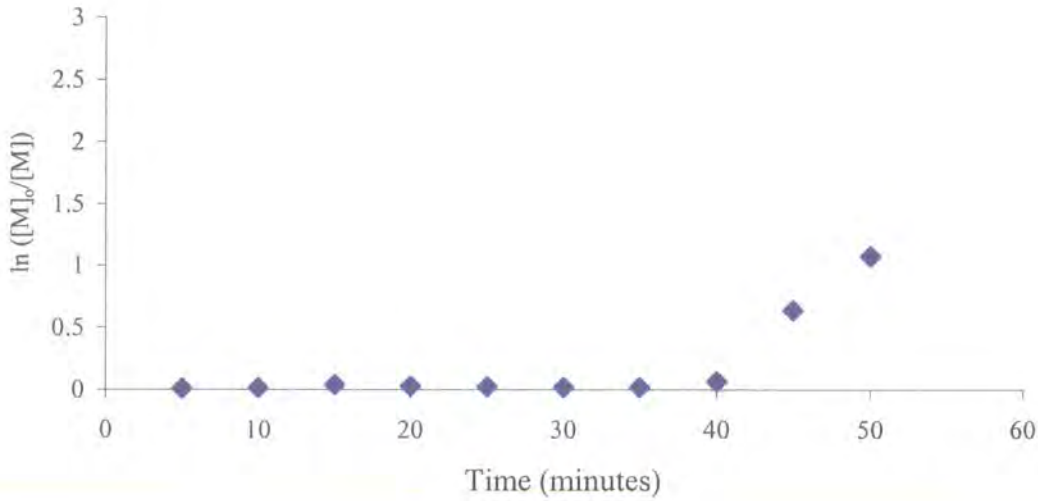

Figure 114 Alkoxyamine 8 initiated *n*-butyl acrylate polymerisation at 125°C with 10% added excess of nitroxide

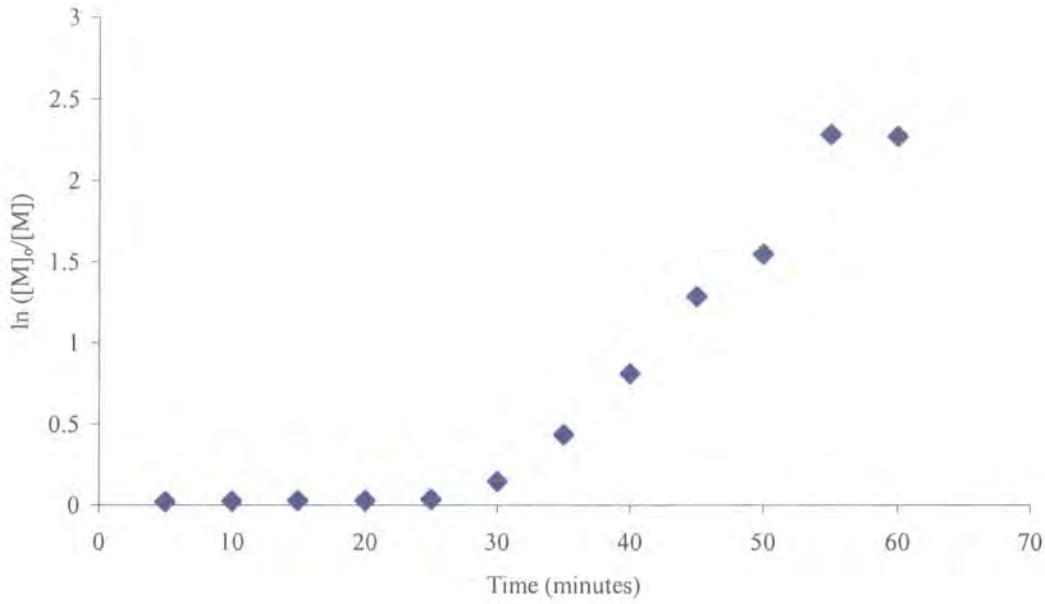

Figure 115 Alkoxyamine 8 initiated *n*-butyl acrylate polymerisation at 125°C with 2% added excess of nitroxide

Gel permeation chromatography **[Figure 116]** of the products of the polymerisation in the presence of 2% excess nitroxide shows no significant increase in number average molecular weight and an increase in polydispersity index with conversion indicative of poor macromolecular control.

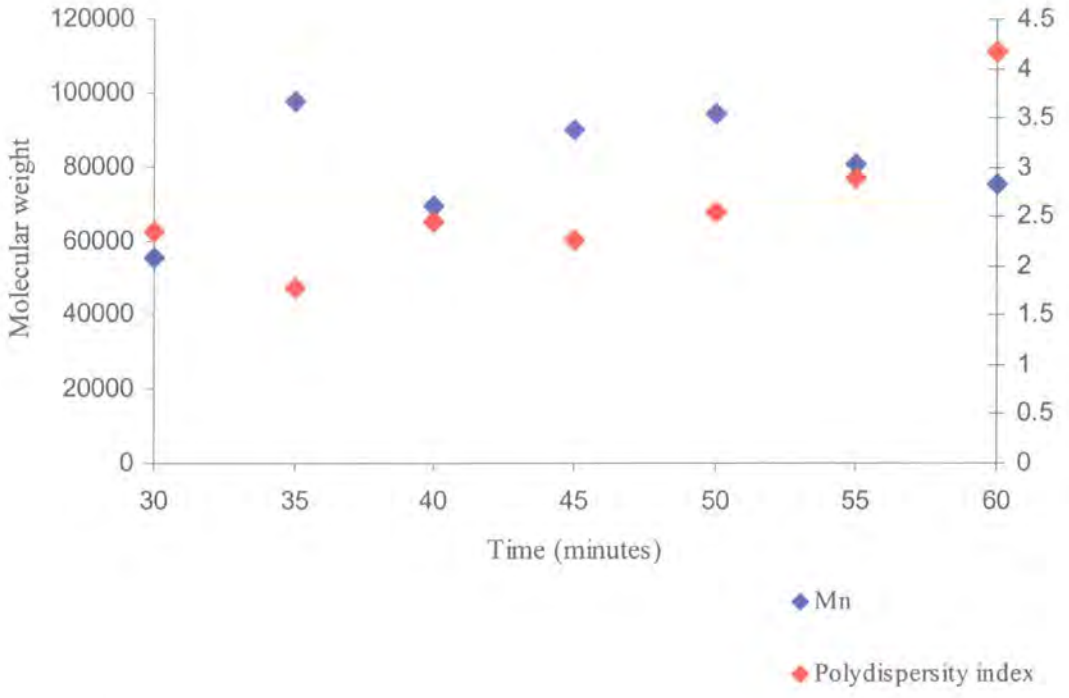

Figure 116 Molecular weight data for alkoxyamine 8 initiated *n*-butyl Acrylate polymerisation at 125°C with 2% excess nitroxide

It was considered that this deviation from the increasing number average molecular weight and decreasing polydispersity index with time might result from an increase in branching of the *n*-butyl acrylate polymer backbone with increasing conversion through transfer of active chain ends to polymer backbone [Figure 117].

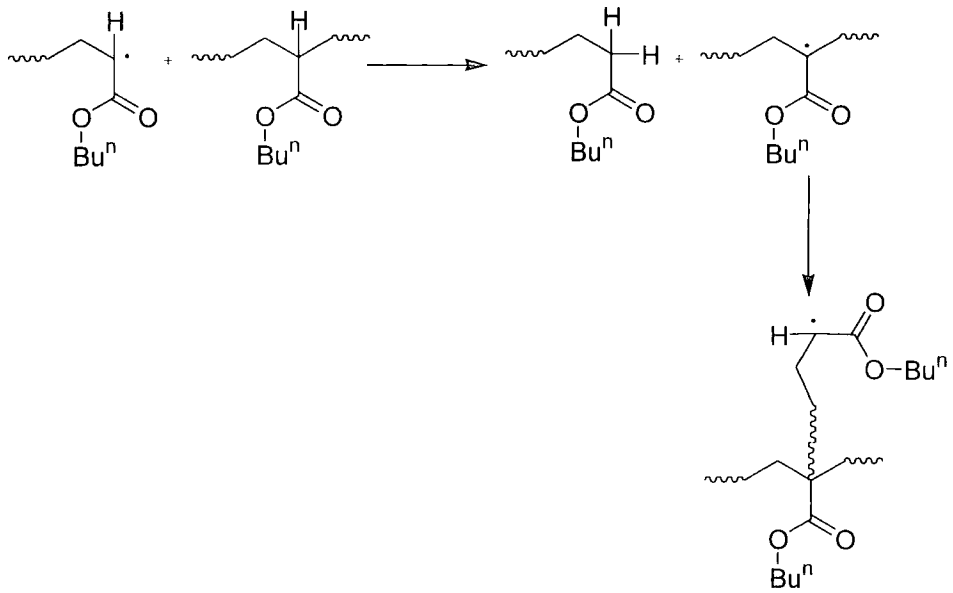

Figure 117 Transfer reaction in butyl acrylate

This increase in branching with increasing conversion has been observed previously[187] by Lovell *et al.* in polymerisations of *n*-butyl acrylate by atom transfer and nitroxide mediated controlled radical polymerisations, in bulk or in mini-emulsion by quantitative ^{13}C NMR spectroscopy[188]. Similar analysis was performed on poly(*n*-butyl acrylate) prepared by alkoxyamine **8** initiated polymerisation. At 46% conversion examination of the NMR spectrum shows the presence of small signals at 39 and 48ppm. Following the assignments of these signals described by Lovell *et al.*, these can be attributed to CH_2/CH and quaternary carbons respectively of monomer units adjacent to branching points indicating that a little branching is occurring within the polymerising system. At 12% conversion these signals in the quantitative carbon spectra cannot however be distinguished. The extent of branching however is very small and does not account for the molecular weight data obtained.

[187] Ahmad, N.M., Heatley, F., Lovell, P.A., Macromolecules, **1998**, 31, 2822-2827

[188] Farcet, C., Bellaney, J., Charleux, B., Pirri, R., Macromolecules, **2002**, 35, 4912-4918

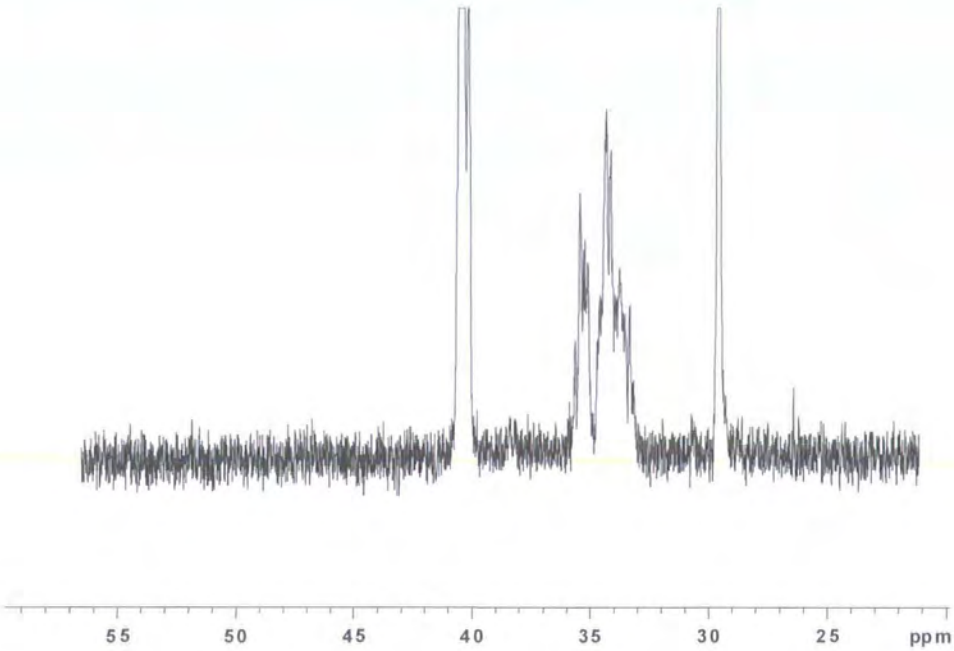

Figure 118 C^{13} spectrum of poly(*n*-butyl acrylate) at 12% conversion

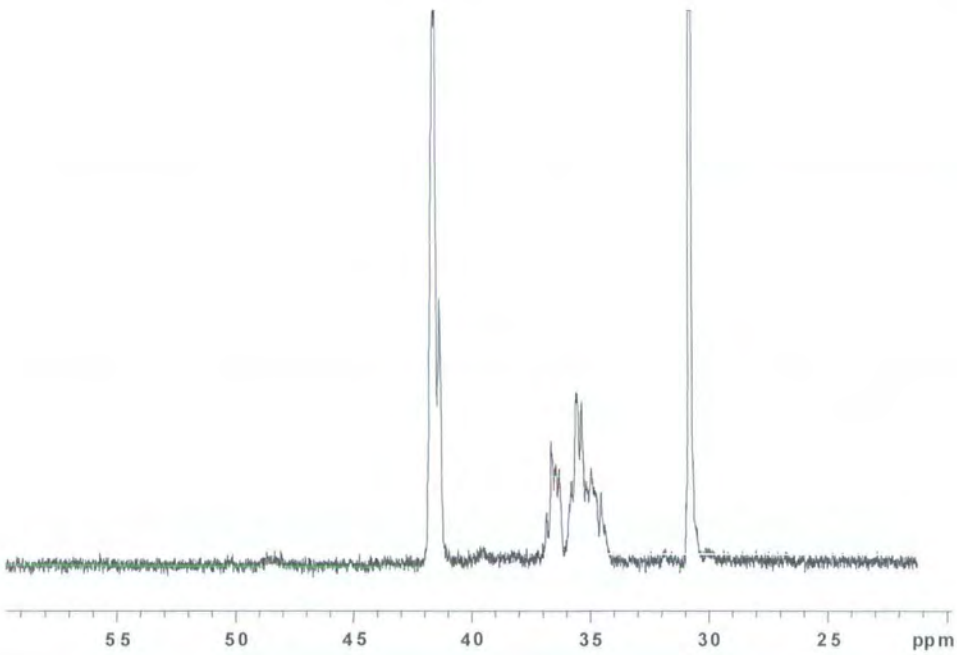

Figure 119 C^{13} spectrum of poly(*n*-butyl acrylate) at 42% conversion

The polymer morphology resulting from branching in *n*-butyl acrylate polymerisation is complicated as this can occur by inter- or intra- molecular transfer. The relative proportions of intra- and inter-molecular transfer in solution polymerisation were observed by Lovell *et al.* to be concentration dependent with intramolecular transfer predominating in dilute solution while intermolecular transfer becomes more significant as concentration increases. Studies by Charleux *et al.* in bulk and miniemulsion polymerisation concluded that the dominant transfer process is through intramolecular backbiting although whether the disparity between these conclusions is a result of concentration effects or temperature is unclear as Lovell's work was performed at 70°C while Charleux studied polymerisation at 112°C. The extent of branching observed within this work does not however account for the poor level of macromolecular control.

In order to investigate the living nature of *n*-butyl acrylate polymer produced by alkoxyamine **8** initiated free radical polymerisation, the polymerisation of styrene was studied at 125°C in the presence of poly(*n*-butyl acrylate) prepared without addition of any excess nitroxide.

The styrene logarithmic conversion index [Figure 120] can be seen to increase with time reaching 50% conversions after four hours.

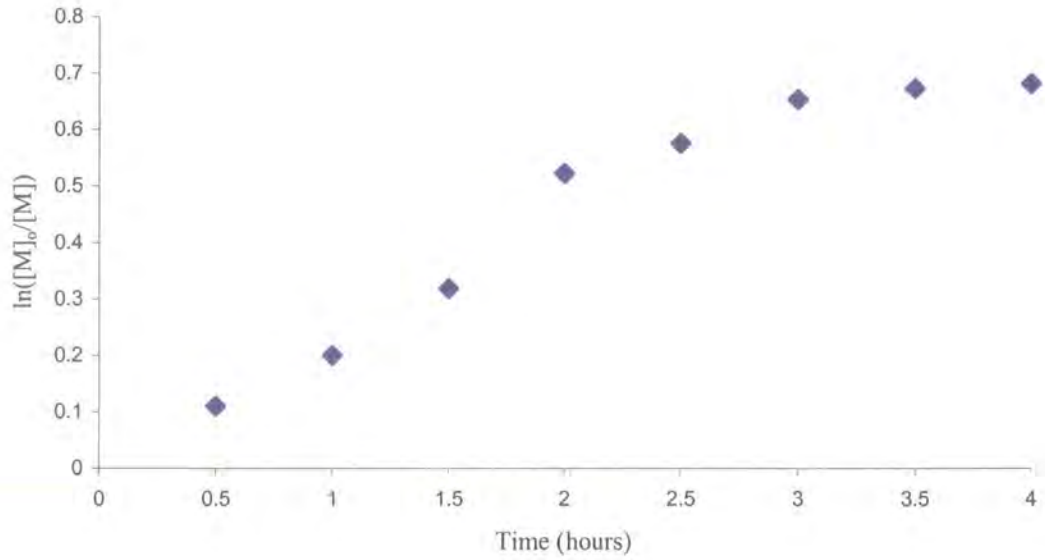

Figure 120 Styrene polymerisation initiated by butyl acrylate at 125°C

Gel permation chromatography of the resulting polymer samples [Figure 122] showed a monomodal molecular weight distribution with increasing number average molecular weight with conversion and a decreasing polydispersity with time.

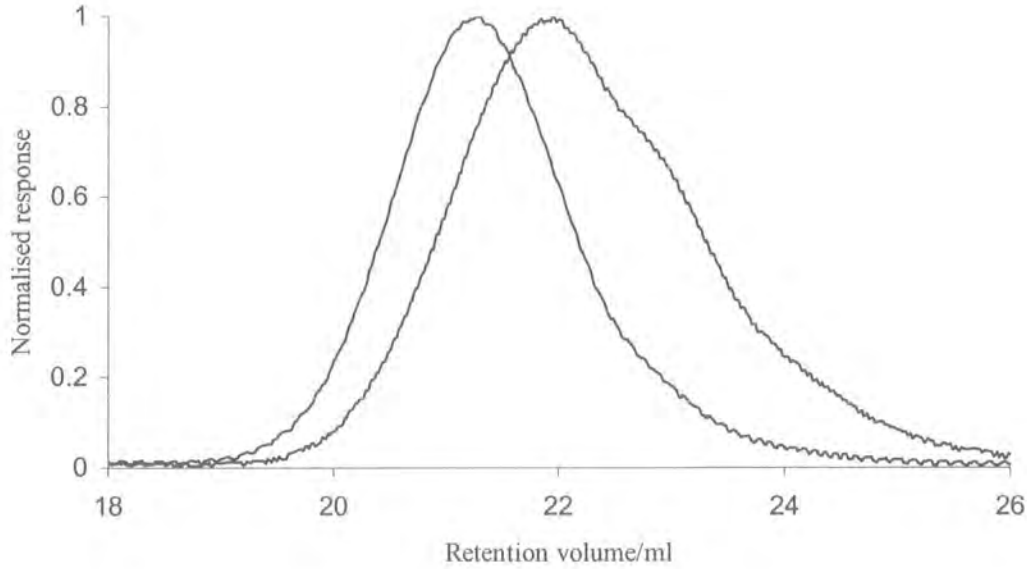

Figure 121 Size exclusion chromatography traces for a poly(*n*-butyl acrylate-*b*-styrene) copolymer and the original poly(*n*-butyl acrylate) macroinitiator (right hand trace).

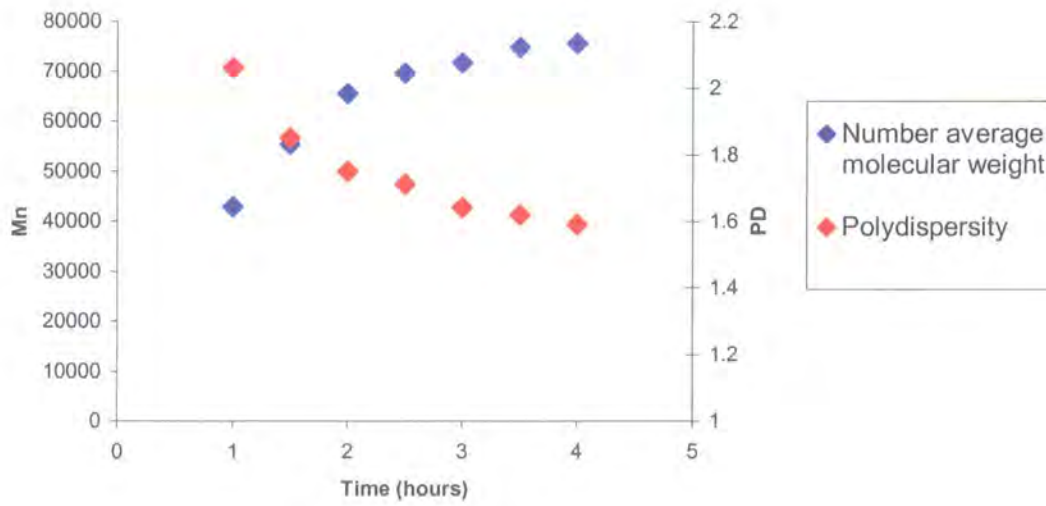

Figure 122 Size exclusion chromatography of *n*-butyl acrylate/styrene block copolymer

Summary

Experiments would indicate that it is possible to initiate polymerisation of *n*-butyl acrylate with alkoxyamine **8** in marked contrast to the alkoxyamine **6**. The rate of this polymerisation may be varied through the introduction of a small excess of the mediating nitroxide species. The resulting polymerisation was however shown to be uncontrolled as evinced by poor control of polydispersity although this polymerisation is suggested to have a living character as the resulting polymer may be used to initiate further polymerisation to generate a copolymer.

Chapter 5 - ESR bond strength studies

Introduction

The study and understanding of factors influencing alkoxyamine bond homolysis have been shown extensively to be of some significance in efforts to improve the design of alkoxyamine unimolecular initiators, accelerating reaction rates and extending the scope of monomer species which can be polymerised by nitroxide mediated free radical polymerisations.

The thermal homolysis reaction of the carbon to oxygen alkoxyamine bonds to produce a stable nitroxide and transient radical is thought to be an endothermic reversible reaction which from the Hammond postulate is likely to have a late transition state, i.e. the transition state is likely to be "product like" with the carbon to oxygen alkoxyamine bond greatly elongated. The reaction profile of this thermolysis is predicted to be of the form shown [Figure 123].

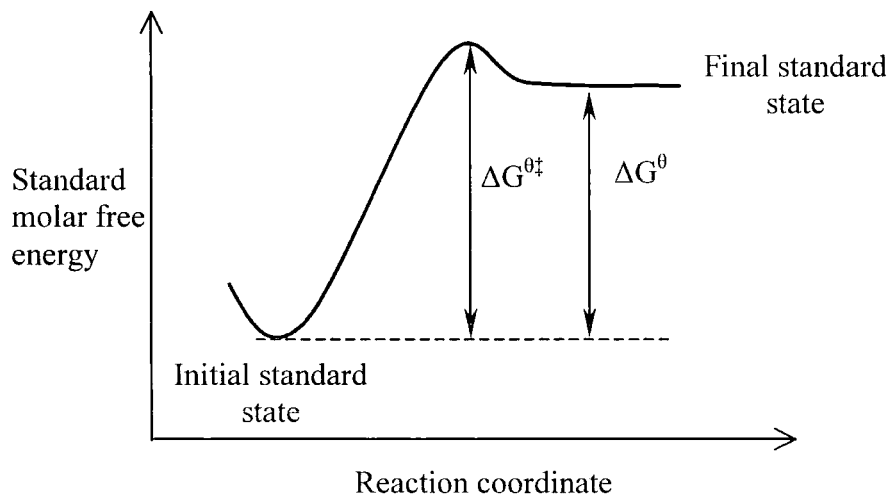

Figure 123 Reversible endothermic reaction reaction coordinate

The instability of alkoxyamine to homolysis of the carbon to oxygen bond was first proposed in studies[189] examining the thermal stability in solution of the product alkoxyamine from nitroxide trapping of a 1,1 diphenylethyl alkyl radical species by 2,2,6,6-tetramethyl-4-oxo-1-(1,1 diphenylethoxy) piperidine. It was observed that upon heating of alkoxyamine solutions an EPR signal indicative of free nitroxide was detected. The EPR signal intensity, which is directly related to nitroxide concentration, was shown vary reversibly with temperature. It was proposed that, in the absence of side reactions, an equilibrium [Figure 124] exists between radical trapping by nitroxide and alkoxyamine homolysis reactions.

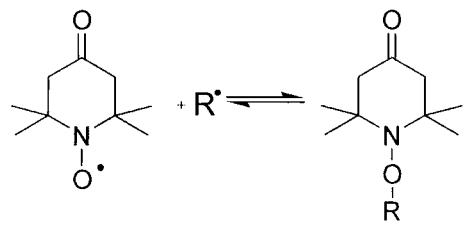

Figure 124 Alkoxyamine equilibrium between radical trapping and thermal homolysis

Studies have been carried out by a number of groups into effect of nitroxide structure on radical trapping[190&191] and alkoxyamine homolysis[192-195] reactions emphasising the importance of steric bulk and electronic structure of the nitroxide mediating radical in determining the rate constants for alkoxyamine carbon to oxygen bond dissociation and nitroxide trapping of propagating radicals.

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[189] Howard, J.A., Tait, J.C., J. Org. Chem., 43, 22, **1978**, 4279-4283

[190] Bowry, V.W., Ingold, K.U., J. Am. Chem. Soc., **1992**, 114, 4992-4996

[191] Skene, W.G., Scaiano, J.C., Listigovers, N.A., Kazmaier, P.M., Georges, M.K., Macromolecules, **2000**, 33, 5065-5072

[192] Moad, G., Rizzardo, E., Macromolecules, **1995**, 28, 8722-8728

[193] Kazmaier, P.M., Moffat, K.A., Georges, M.K., Veregin, R.P.N., Hamer, G.K., Macromolecules, **1995**, 28, 1841-1846

Studies[196] into the homolysis of polymeric alkoxyamines have achieved varied results with German *et al.*[197] reporting a large increase in the rate measured by quantitative ESR studies of TEMPO nitroxide release from alkoxyamines, in polymeric alkoxyamine species compared to small molecules alkoxyamines. This was largely ascribed to entropic effects. This is in contrast to the work of Fukuda[198,199] who, using a GPC resolution method, examined the loss of an initiating polymeric alkoxyamine adduct with time in the early stages of polymerisation, to calculate the rate of activation. GPC chromatography allows separation of the original adduct and those chains which have undergone homolysis and propagation. These studies resulted in calculation of a homolysis rate two to three times larger than that calculated by Fischer for comparable small molecule alkoxyamine species based on the same TEMPO, DBN and DEPN nitroxides. Gnanou *et al.*[200] using the same GPC approach as Fukuda obtained thermodynamic parameters for the DEPN nitroxide polymeric adduct almost identical to those obtained by Fischer for small alkoxyamine systems with the same nitroxide. In an attempt to resolve this confused

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[194] Marsal, P., Roche, M., Tordo, P., de Sainte Claire, P., J. Phys. Chem. A., **1999**, 103, 2899-2905

[195] Marque, S., Le Mercier, C., Tordo, P., Fischer, H., Macromolecules, **2000**, 33, 4403-4410

[196] Marque, S., Fischer, H., Baier, E., Studer, A., J. Org., Chem., **2001**, 66, 1146-1156

[197] Bon, S.A.F., Chambard, G., German, A.L., Macromolecules, **1999**, 32, 8269-8276

[198] Goto, A., Fukuda, T., Macromol. Chem. Phys., **2000**, 201, 2138-2142

[199] Goto, A., Kwak, Y., Yoshikawa, C., Tsujii, Y., Sugiura, Y., Fukuda, T., Macromolecules, **2002**, 35, 3520-3525

[200] Benoit, D., Grimaldi, S., Robin, S., Finet, J-P, Tordo, P., Gnanou, Y., J. Am. Chem. Soc. 122, 25, **2000**, 5929-5939

issue Tordo *et al.*[201] studied by quantitative ESR measurements the effect of polymeric chain length on SG1 nitroxide alkoxyamine homolysis as a function of chain length, which obtained no clear influence of the chain length.

The SG1 and TIPNO nitroxides have been shown to have the highest observed alkoxyamine dissociation rate constant at polymerisation temperatures. These nitroxides have also been demonstrated as the most effective mediating species applied to date in styrene polymerisation and extension of nitroxide mediated controlled radical polymerisation of other monomers, such as acrylates. Fisher, examining the rate constants for monomer propagation, nitroxide capping and homolysis values showed that the equilibrium constant between capping and homolysis reactions for SG1 and TIPNO nitroxide are within the conditional limits such that persistent radical effect kinetic scheme is applicable.

In order to investigate the improved rates observed through the use of alkoxyamine **2** in the polymerisation of styrene compared to alkoxyamines and and the success of this alkoxyamine in initiating *n*-butyl acrylate polymerisation, the thermal homolyses of carbon to oxygen bonds of alkoxyamines **6, 7, 8, 11** and **12** based on these nitroxides **5, 1** and **2** were studied. The nitroxides and alkoxyamines under study were prepared and purified as described in chapter 2.

[201] Bertin, D., Chauvin, F., Marque, S., Tordo, P., Macromolecules, **2002**, 35, 10, 3790-3791

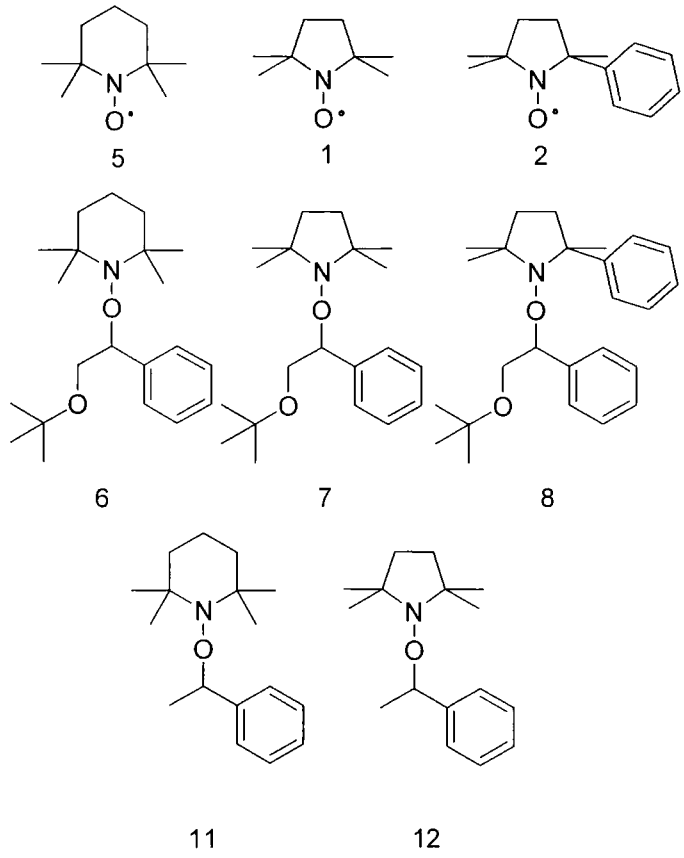

Figure 125 Alkoxyamines and nitroxides

Experimental

Standards

Standard solutions of nitroxides **1, 2** and **5** were prepared in distilled toluene. These solutions were placed in turn to constant depth in an ESR tube and the top of the tube sealed with parafilm to minimise solvent evaporation. The tube was then placed in the ESR spectrometer and allowed to equilibriate thermally; the ESR signal was then measured. A series of measurements was made over time to confirm the stability of each sample. The same tube was used throughout the series of experiments to ensure consistency.

Alkoxyamine Decomposition

Solutions were made up of the five alkoxyamines, **6**, **7**, **8**, **11** and **12**, under study based on nitroxides, **1**, **2** and **5**. These solutions were placed to the same depth as the previous standards nitroxide solutions in the ESR tube and the top of the tube sealed with parafilm to minimise evaporation. The ESR spectrometer was tuned at room temperature and the tube removed while the spectrometer thermally equilibrated at elevated temperature. At time zero the tube was placed in the spectrometer, the spectrometer retuned and spectra obtained at regular intervals thereafter. No attempt was made to degas the the samples in order to maintain irreversible conditions in which an excess of dissolved oxygen is used as a competing radical trap to prevent the reverse capping reaction.

(ESR) sometimes referred to as electron paramagnetic resonance (EPR) which gives a direct measurement of nitroxide concentration without requiring offline sampling was selected as the most direct method of studying alkoxyamine homolysis. ESR is a similar and complementary technique to nuclear magnetic resonance in that it examines the interaction of unpaired spin with electromagnetic radiation although rather than nuclear spin it is the spin associated with unpaired electrons that is the subject of study. The requirement that the sample under investigation contain unpaired electron spin means that only certain species are suitable for study, including radicals, many d-metal complexes and molecules in triplet states.

In a magnetic field the energy levels of an electron where $m_s = \pm\frac{1}{2}$ are given by [**Equation 27**]

$$E_m = g_e \mu_B m_s B$$

Equation 27

The energy of an α electron is increased relative to that of the ground state while that of a β electron is decreased accordingly [Figure 126] with the energy level separation given by [Equation 28]

$$\Delta E = g_e \mu_B B$$

Equation 28

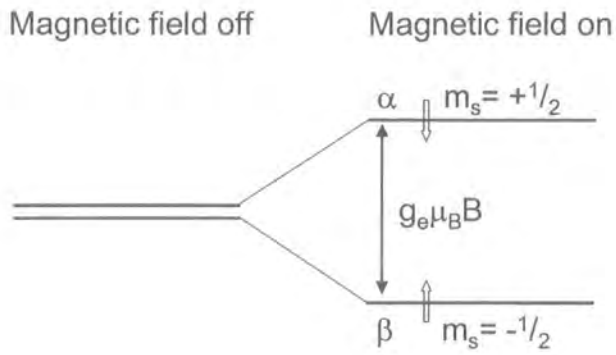

Figure 126 Energy level splitting for electrons in a magnetic field

A typical spectrometer consists of a microwave source or klystron, a sample cavity and a variable field electromagnet [Figure 127] and operates by observing the magnetic field at which an unpaired spin comes into resonance with a monochromatic source of radiation. An ESR spectrum is obtained by monitoring the microwave absorption of the sample as the field is varied. The ESR spectrum is normally presented as the first derivative of the absorption.

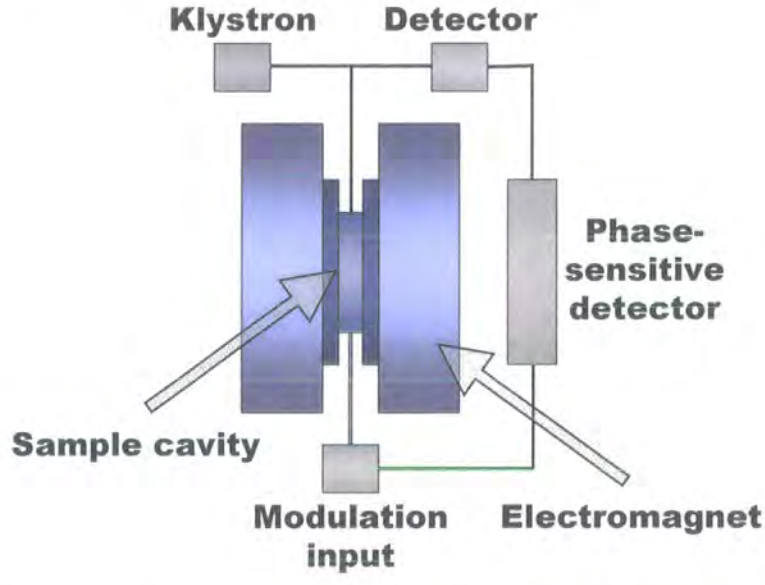

Figure 127 Schematic representation of a typical electron spin resonance spectrometer

The centre of the ESR signal allows us to calculation of the *g* value of the radical or complex which is, in a sense, analogous to the chemical shift in a NMR spectra. The *g* value is determined by the susceptibility of the radical to the formation of local electron currents resultant from the applied field. The principal use of the *g* value is in identifying the chemical species present in a sample although more specific information is limited as the *g* values measured for organic radicals are very similar. Further information is obtained from hyperfine splitting of the ESR spectrum, which is a consequence of the interaction between the electron spin and the magnetic dipole moments of nuclei present in the sample. In the case of hydrogen, spin ½, this interaction results in splitting of the ESR spectrum into a doublet while with nuclei such as nitrogen, spin 1, this would result in splitting into a triplet. The hyperfine splitting structure is often used as a fingerprint technique for a sample under study.

As a consequence of the detection apparatus the ESR spectrum is obtained as the second derivative of the absorption. The double integral of the spectrum gives information on the total absorption of a sample. The magnitude of the radiation absorption is proportional to the number of molecules possessing unpaired spin contained within the sample cavity. Through measuring the absorption of standards with a known concentration a calibration curve may be constructed for a sample under study allowing translation of a double integral of ESR spectrum into concentration.

Collection of ESR spectra from alkoxyamine samples which are thermally homolysed under irreversible conditions in the presence of an excess alkyl radical trapping species such as dissolved oxygen, with time results in an increasing double integral with time from which a rate of alkoxyamine homolysis may be calculated.

Measurement of alkoxyamine homolyses over a range of temperatures allows construction of an Arrhenius plot and calculation of Arrhenius parameters.

It has been shown for many reactions that the rate constant varies with temperature following the equation [Equation 29]

$$k = Ae^{-E_a/RT}$$

Equation 29

where k = rate constant, E_a is the Arrhenius activation energy, T is the absolute temperature, R is the gas constant and A is a pre-exponential or frequency factor. The values in this relationship may be obtained graphically by plotting ln k or log k against 1/T allowing calculation of A and E_a from the intercept and gradient respectively. These Arhenius terms relate to a theoretical treatment of the reaction rates which from transition state theory gives [Equation 30]

$$E_a = \Delta H^{\theta} + RT$$

Equation 30

From this it is apparent that the Arrhenius activation energy is closely related to the standard energy of activation. Using the mean temperature over which the Arrhenius plot was constructed allows calculation of ΔH^{θ} from experimentally obtained values fro E_a. The frequency factor A can similarly be related [Equation 31] to the standard entropy of activation

$$A = \frac{k_B T}{h} e^{-\Delta G^{\theta}/RT}$$

Equation 31

where T is the mean absolute temperature of the range over which the equation rate constants are determined. The standard molar entropy of activation corresponds to the entropy change between reactants and activated complex.

A range of concentrations of the nitroxides **1**, **2** and **5** under study were used to establish a correlation between double integral of ESR signal and nitroxide concentration [Figures 145-147].

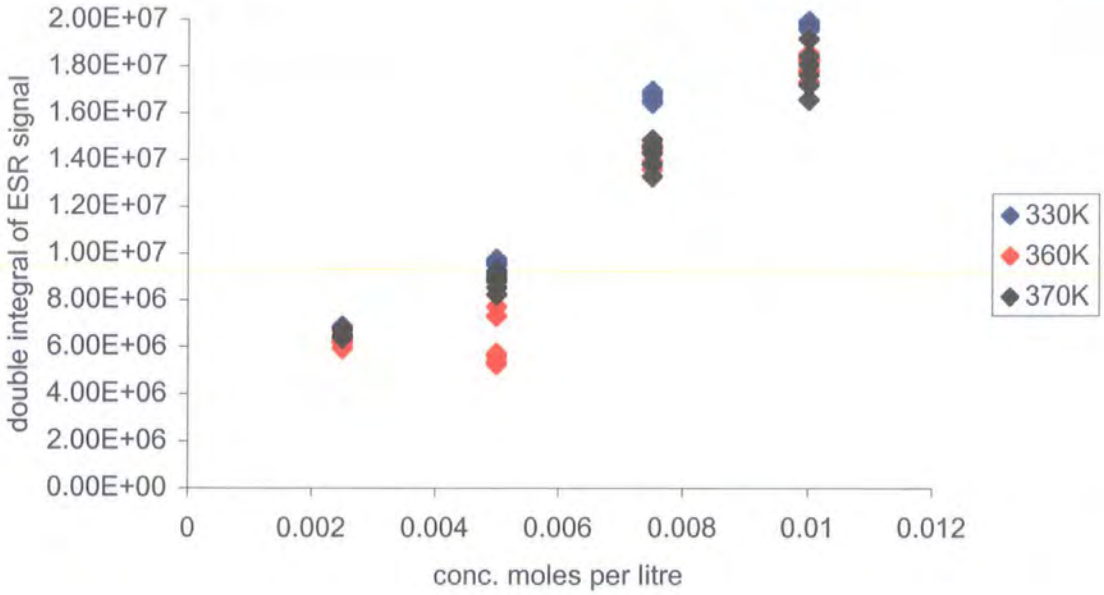

Figure 128 Nitroxide 5, TEMPO Standards

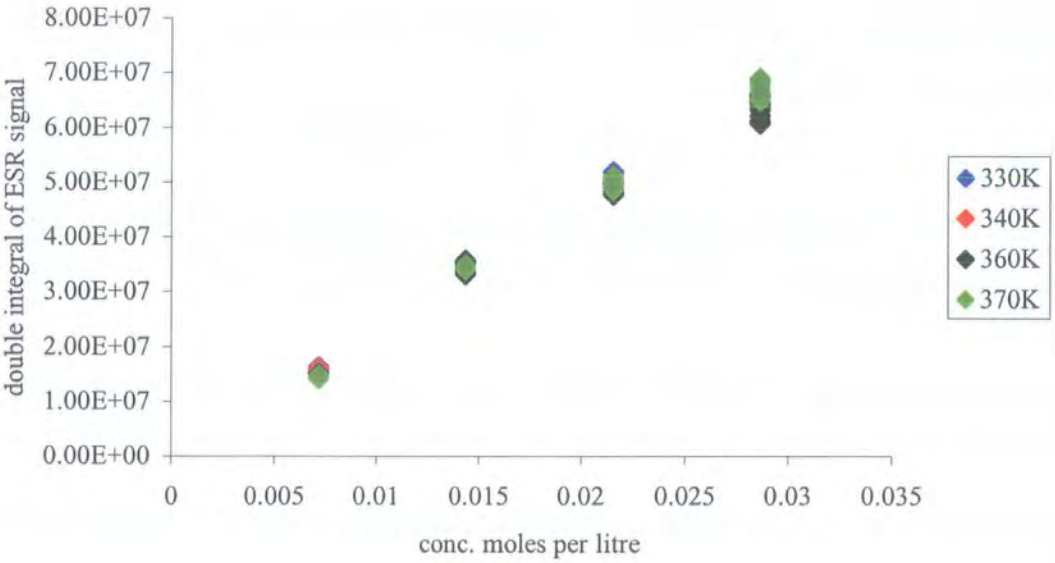

Figure 129 Nitroxide 1 Standards

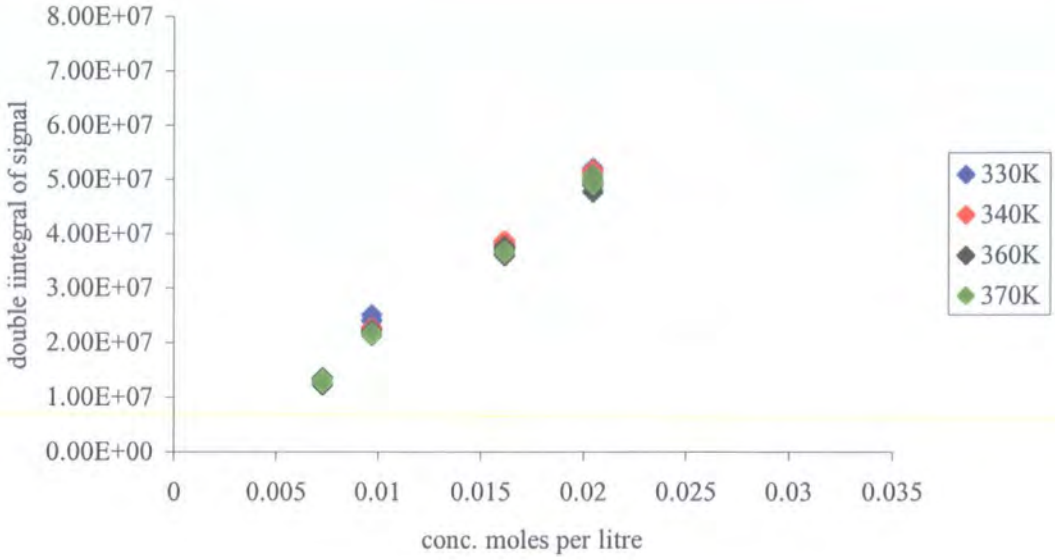

Figure 130 Nitroxide 2 Standards

Applying a linear best fit to the double integral with time data over several temperatures range allows the calculation of alkoxyamine bond homolysis rates and from them construction of an Arrhenius plot for the alkoxyamine system. In those systems in which a plateau was reached the initial linear data points were used to calculate rate. A nonlinear least squares fitting algorithm was used to fit equations to the plots and obtain the Arrhenius parameters for each alkoxyamine.

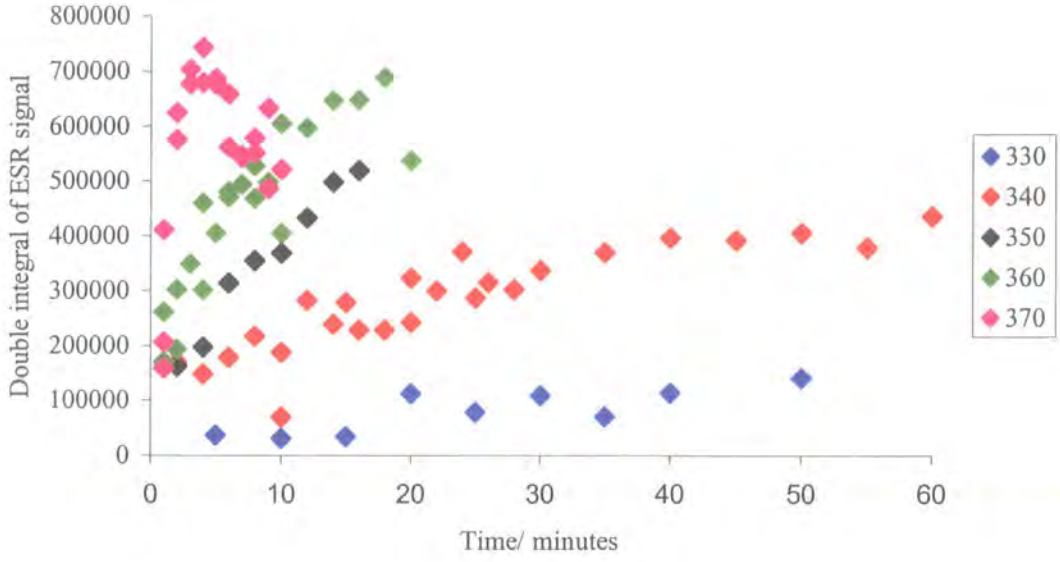

Figure 131 Double integral against time for alkoxyamine 6 homolysis

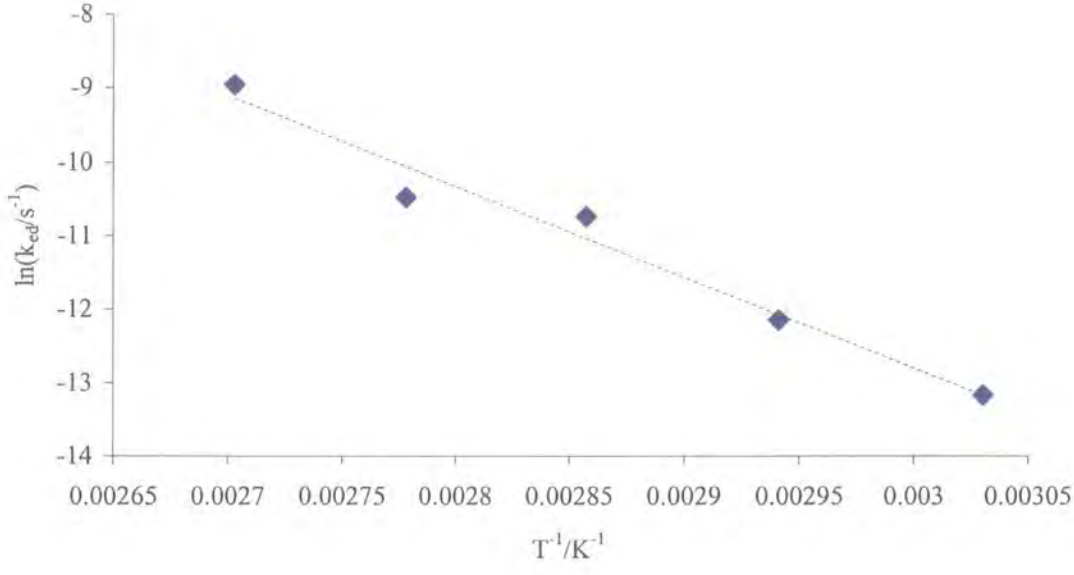

Figure 132 Arrhenius plot for alkoxyamine 6 homolysis

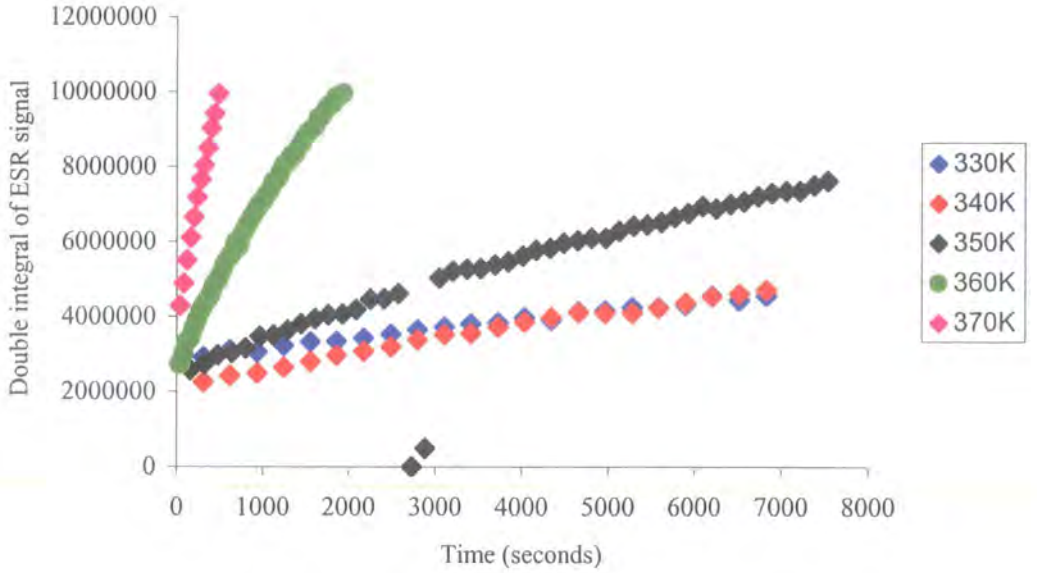

Figure 133 Double integral against time of alkoxyamine 7 homolysis

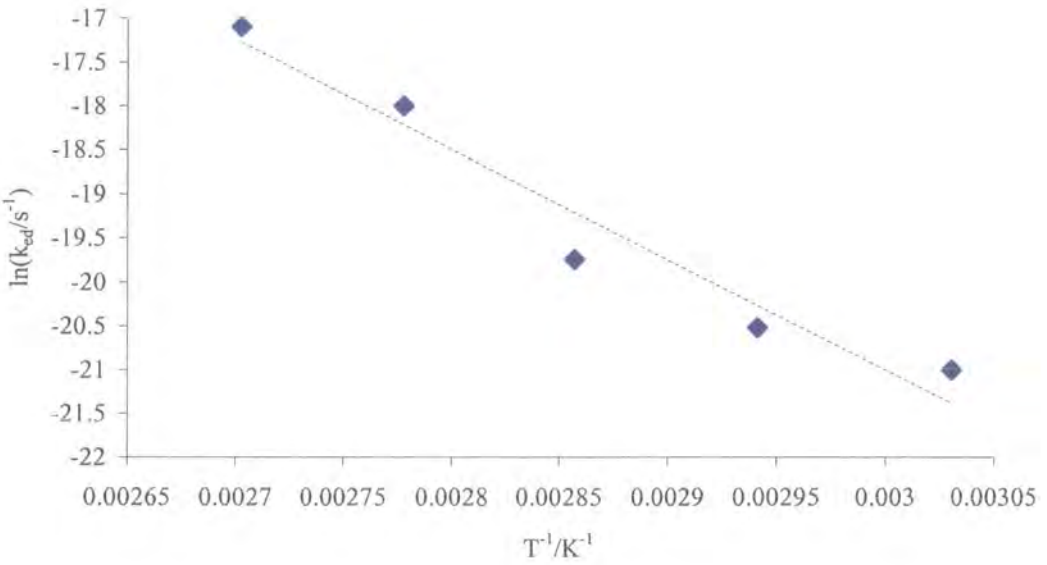

Figure 134 Arrhenius plot for alkoxyamine 7 homolysis

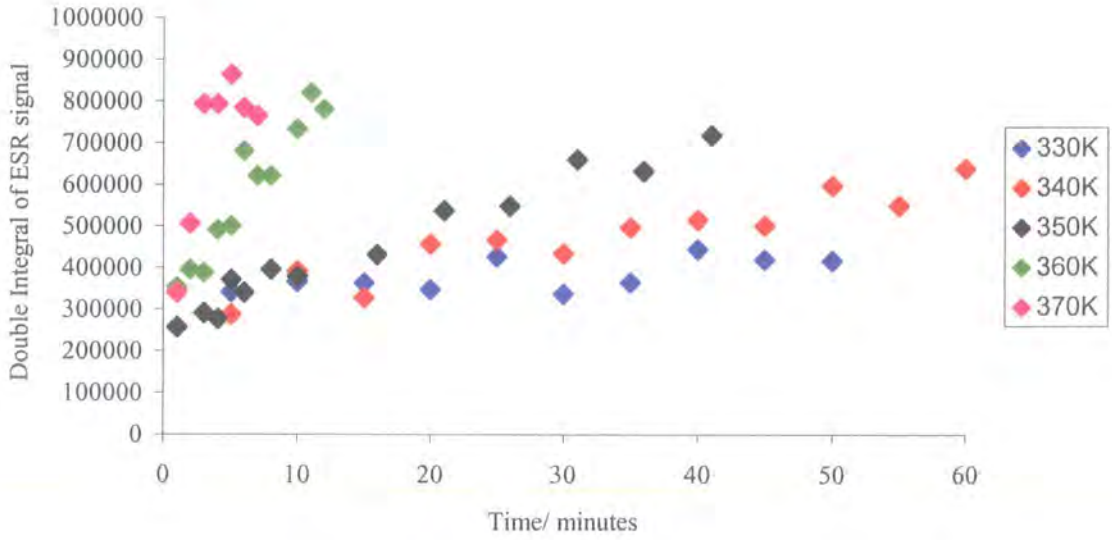

Figure 135 Double integral against time for alkoxyamine 8 homolysis

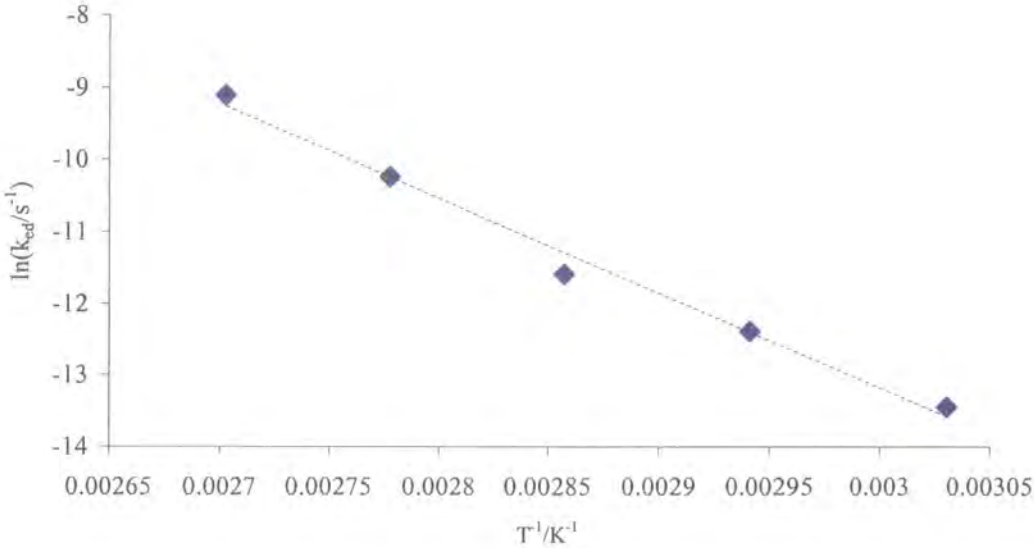

Figure 136 Arrhenius plot for alkoxyamine 8 homolysis

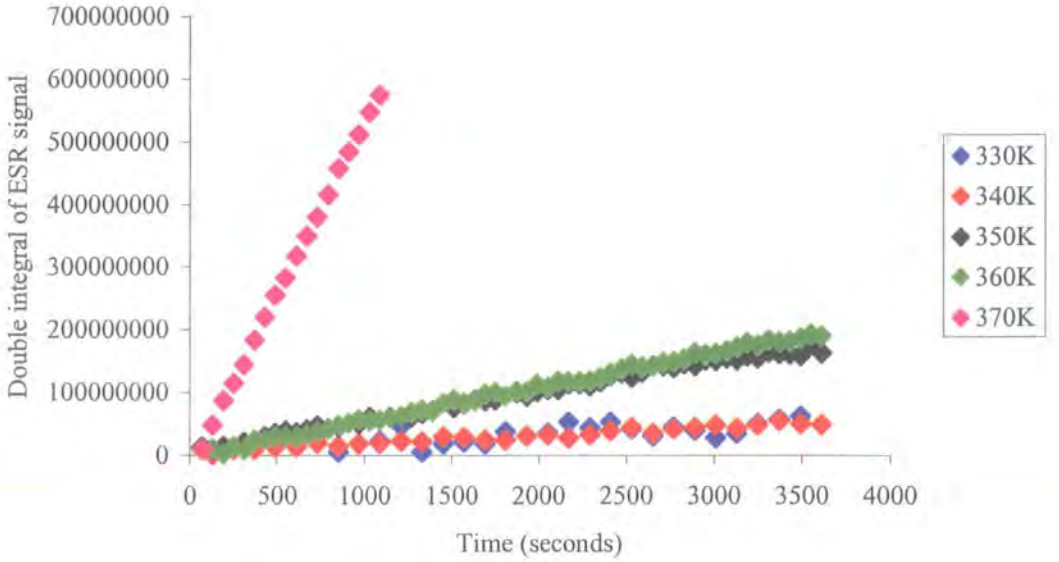

Figure 137 Double integral against time for alkoxyamine 11 homolysis

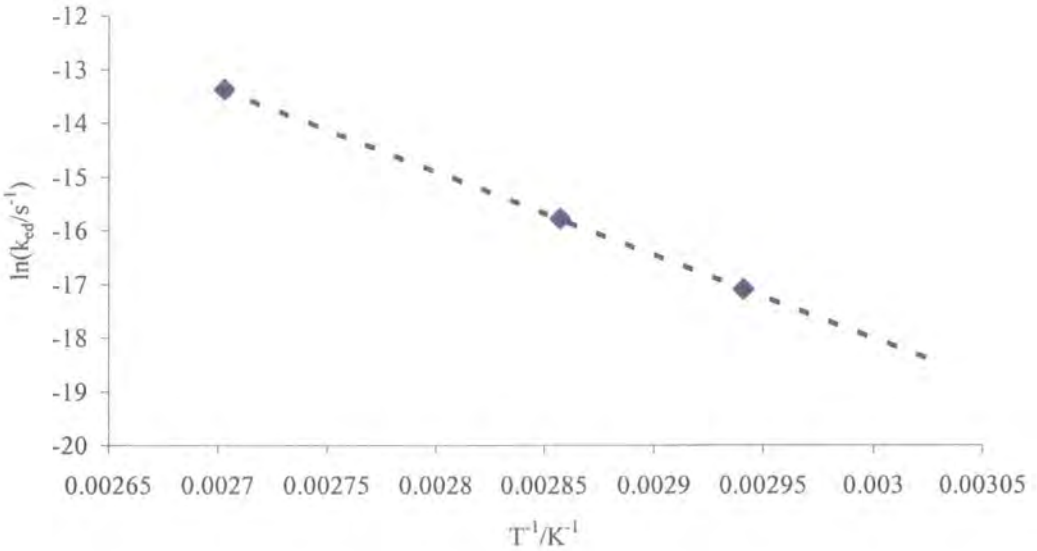

Figure 138 Arrhenius plot for alkoxyamine 11 homolysis

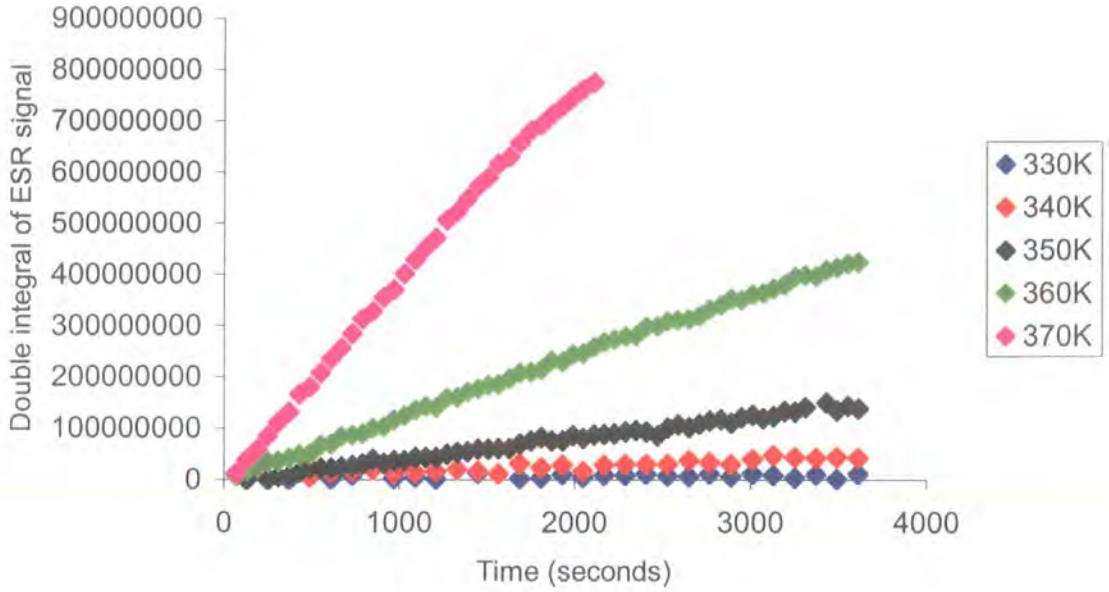

Figure 139 Double integral against time for alkoxyamine 12 homolysis

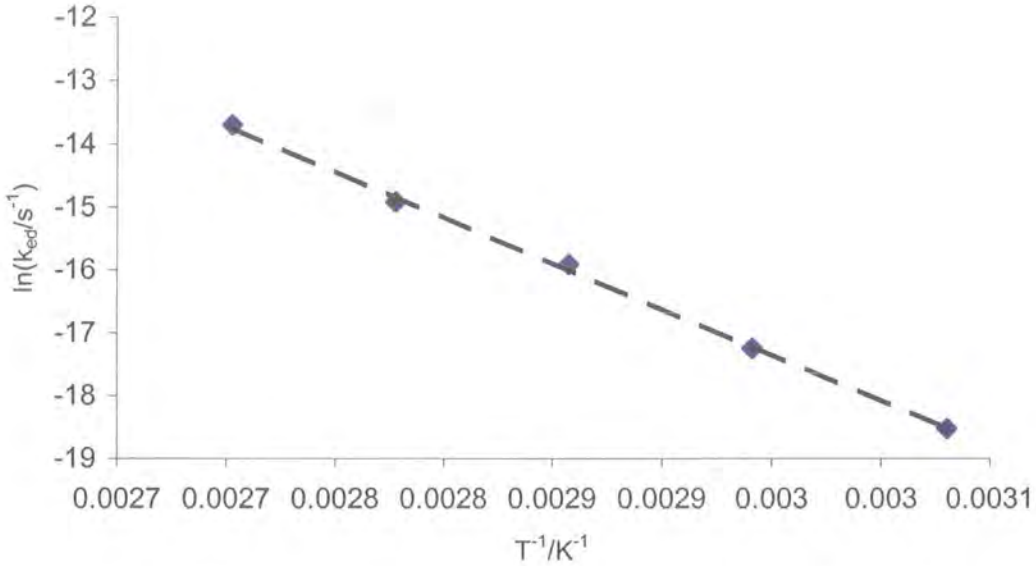

Figure 140 Arrhenius plot for alkoxyamine 12 homolysis

Placing the fitted Arrhenius parameters for the alkoxyamines in a table we can compare the behaviour of different nitroxides.

Alkoxyamine	A (s^{-1})	E_a ($kJmol^{-1}$)
6	$3.20x10^{10}$	102.5
7	$2.00x10^{9}$	104.3
8	$2.05x10^{11}$	109.8
11	$3.23x10^{14}$	129.9
12	$1.61x10^{13}$	121.8

The calculated Arrhenius pre-exponential and bond strengths obtained are similar to those obtained by other groups on comparable alkoxyamines. However since reported values vary between different groups and experimental methods each study is best viewed as being a self consistent data set.

With alkoxyamines prepared through nitroxide trapping of the radicals resulting from reaction of di-*tert*-butyl peroxalate with styrene the obtained rates of dissociation show a large decrease on changing from the 6-membered nitroxide 5, TEMPO, ring to the five membered nitroxide **2** analogue as might be expected from previous studies into the effect of nitroxide steric bulk. The substitution of the five membered ring with a phenyl substituent in the 2 ring position in nitroxide **3** led to an increased rate of dissociation to slightly less than that for the alkoxyamine derived from TEMPO.

Comparison of the dissociation energies for alkoxyamines prepared via the two synthetic routes described in chapter 2 show that those alkoxyamines derived from the di-*tert*-butyl peroxalate synthetic route had lower dissociation energies than those synthesised via the epoxidation catalyst route presumably as aresult of increased steric bulk of the styryl residue.

Summary

Measurement of alkoxyamine carbon oxygen bond homolysis rates were measured utilising ESR allowing calculation of the activation energies for this homolysis. The small differences activation energies for dissociation and homolysis rates do not appear to explain the enhanced rates of polymerisation which have been observed in the styrene polymerisation initiated by alkoxyamine **8** or the activity of this alkoxyamine in initiation of *n*-butyl acrylate polymerisation.

Chapter 6 - Hydrogen Transfer Disproportionation

Introduction

The potential for alkoxyamine species to undergo a disproportionation reaction was noted by Howard *et al.*[202] in studies examining the thermal stability of 2,2,6,6-tetramethyl-4-oxo-1-(1,1-diphenylethoxy)piperidine [Figure 141] in solution.

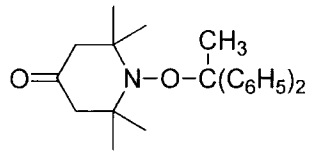

Figure 141 2,2,6,6-tetramethyl-4-oxo-1-(1,1-diphenylethoxy)piperidine

Heating of a degassed solution of this alkoxyamine in *tert*-butyl benzene was observed by ESR spectroscopy to result in the observation of an ESR signal indicative of the formation of nitroxide, the signal intensity and correspondingly nitroxide concentration was shown to vary reversibly with temperature. A reversible homolysis reaction was proposed in which alkoxyamine carbon to oxygen bond homolyses thermally to produce nitroxide and carbon centred radicals, which may react to regenerate alkoxyamine [Figure 142].

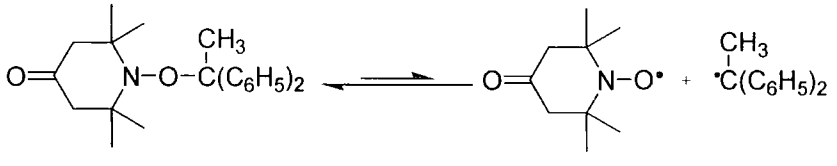

Figure 142 Reversible homolysis of alkoxyamine

Heating a degassed chloroform solution of the alkoxyamine was observed to give a quantitative yield of the corresponding hydroxylamine and 1,1-diphenylethylene.

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[202] Howard, J.A., Tait, J.C., J. Org. Chem., **1978**, 43, 22, 4279-4283

Heating an alkoxyamine chloroform solution without any degassing step was seen to give a near quantitative yield of nitroxide and a mixture of acetophenone, benzophenone and 1,1-diphenyl ethanol. The change in products from a degassed sample was suggested to be a consequence of reaction between dissolved oxygen and the carbon centred radicals generated by alkoxyamine homolysis.

In order to confirm this proposition a non-degassed sample was heated with the addition of the free radical scavenger 2,6-di-*tert*-butyl-4-methyl phenol. This resulted in the formation of nitroxide, 1,1-diphenyl ethyl hydroperoxide and 2,6-di-tert-butyl-4-methyl-4-(1,1-diphenyl ethyl peroxy)-2,5-cyclohexadiene-1-one the formation of which supports the trapping by oxygen of carbon centred radicals from alkoxyamine homolysis via the reaction sheme shown [Figure 143].

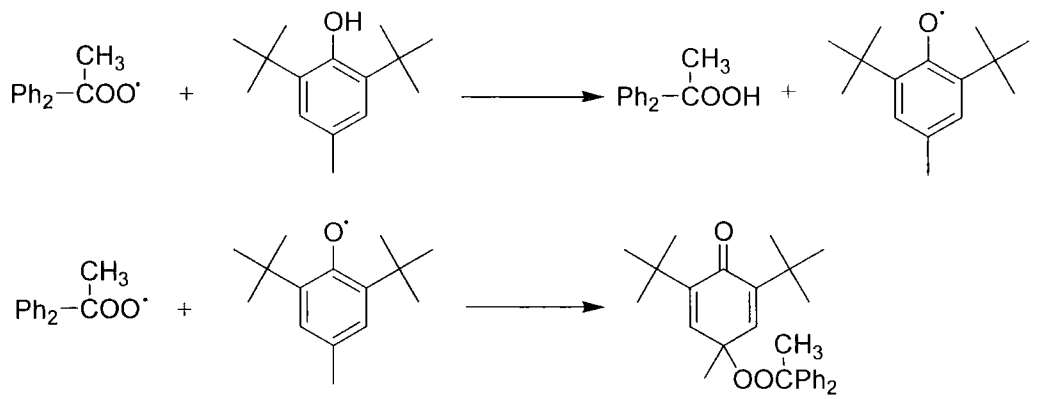

Figure 143 Reactions of peroxy radical species from oxygen trapping in the presence of a hydrogen donor

The thermal decomposition of alkoxyamine was proposed to occur via a reversible homolysis of the alkoxyamine carbon to oxygen bond to generate a nitroxide and a carbon centred radical. It was suggested that these radicals can go on to either recombine to reform the starting alkoxyamine or react via a hydrogen transfer disproportionation reaction to generate a hydroxylamine corresponding to the nitroxide and an unsaturated species. In the presence of an excess auxiliary species

such as dissolved oxygen which can act as alkyl radical trap these reverse trapping and hydrogen transfer reactions are prevented [Figure 144].

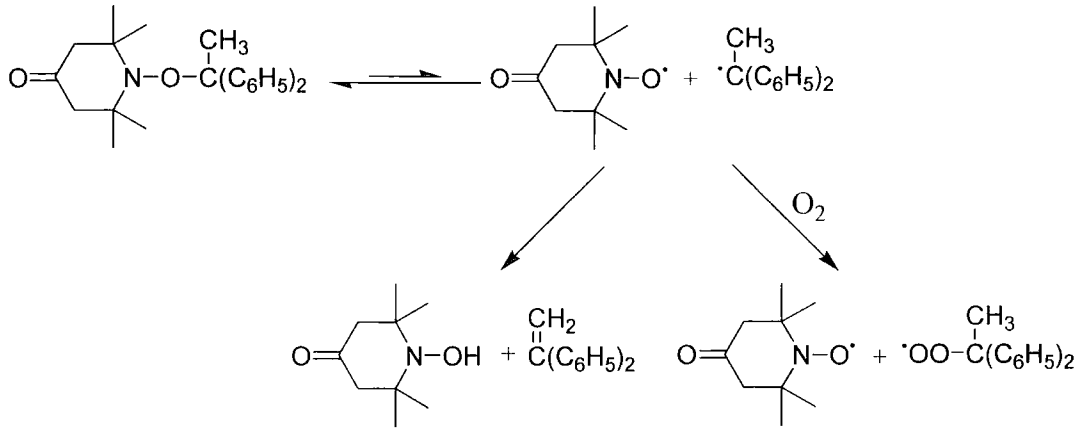

Figure 144 Proposed reaction scheme for thermal homolysis of 2,2,6,6-tetramethyl-4-oxo-1-(1,1-diphenylethoxy)piperidine

Grattan *et al.*[203] similarly studied the thermal decomposition in solution of 1-(2-cyano-2'-cyano-2'-propoxy)-4-oxo-2,2,6,6-teramethylpiperidine [Figure 145].

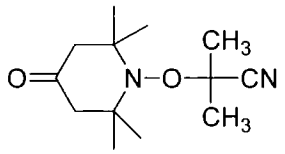

Figure 145 1-(2-cyano-2'-cyano-2'-propoxy)-4-oxo-2,2,6,6-teramethylpiperidine

It was found that heating a degassed alkoxyamine solution resulted in production of a greater than 90% yield of hydroxylamine and approximately 80% yield of methacrylonitrile.

In alkoxyamine solutions without degassing it was observed that the rate of decomposition was some fifty times faster with the major products produced being an 80% yield of nitroxide, 50% yield of 2-cyanopropan-2-ol and acetone. Acetone

[203] Grattan, D.W., Carlsson, D.J., Howard, J.A., Wiles, D.M., Can. J. Chem., **1979**, 57, 2834-2842

was suggested to have been formed by the further decomposition of 2-cyanopropan-2-ol with loss of HCN.

Decompositions reactions in both either degassed and non-degassed solutions were shown to have a strong solvent dependence with accelerated rates of product formation observed with increasing solvent polarity.

Grattan *et al.* proposed a similar reaction scheme [Figure 146] to that suggested by Howard *et al.* for decomposition of the alkoxyamine in which a reversible homolysis reaction occurs to generate a nitroxide and carbon centred radical. The unstable carbon centred radicals can then either recombine with nitroxide to regenerate the starting alkoxyamine, react by biradical combination to form a stable species or react with nitroxide by a disproportionation reaction to generate hydroxylamine and an unsaturated species. In the presence of an excess of an efficient radical trap such as oxygen these combination and disproportionation reactions are prevented and the products obtained are nitroxide and trapping by products.

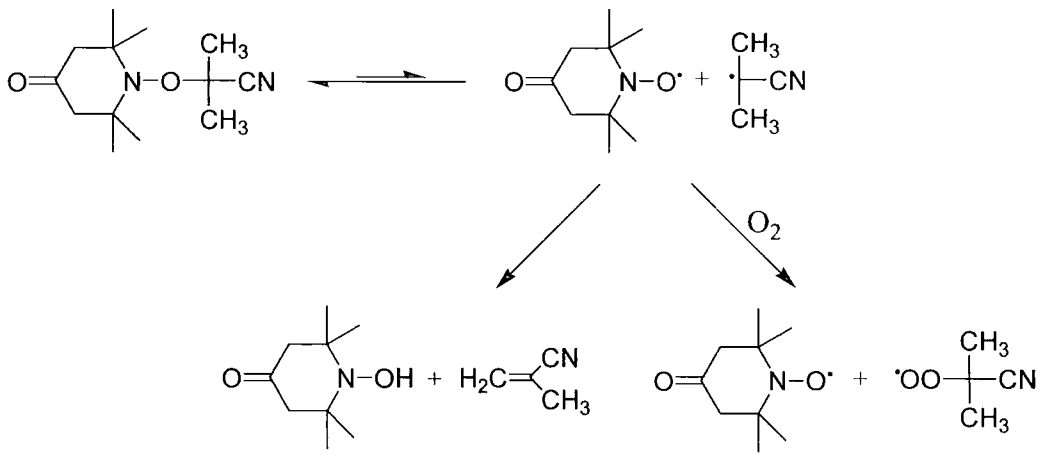

Figure 146 Proposed mechanism for thermal homolysis of 1-(2-cyano-2'-cyano-2'-propoxy)-4-oxo-2,2,6,6-teramethylpiperidine

The findings in this study were contrasted with previous work of Keana *et al.*[204] who observed that the alkoxyamine 1-benzyloxy-4-hydroxyl-2,2,6,6-tetramethyl piperidine, which has no reactive β-hydrogens, is stable at 170°C .

Gridnev[205] examined the effect of hydroxylamines, which were previously understood to be easily oxidised by oxygen or peroxides, formed through hydrogen transfer disproportionation on free radical polymerisation. The addition of hydroxylamines were shown to result in retardation of polymerisation. Through model studies this was suggested to be a consequence of removal of propagating radicals from the polymerisation reduction of carbon centred radicals with corresponding oxidation of hydroxylamine to nitroxide [Figure 147].

Figure 147 Reduction of propagating radical by hyroxylamine

Gridnev suggested that hydroxylamine might participate in catalytic chain termination in which the hydroxylamine product formed by disproprtionation may react with a propagating radical terminating a further chain to generate a saturated chain end with regeneration of the nitroxide [Figure 148].

[204] Keana, J.F.W., Dinerstein, R.J., Bath, F., J. Org. Chem., **1971**, 36, 209,

[205] Gridnev, A.A., Macromolecules, **1997**, 30, 7651-7654

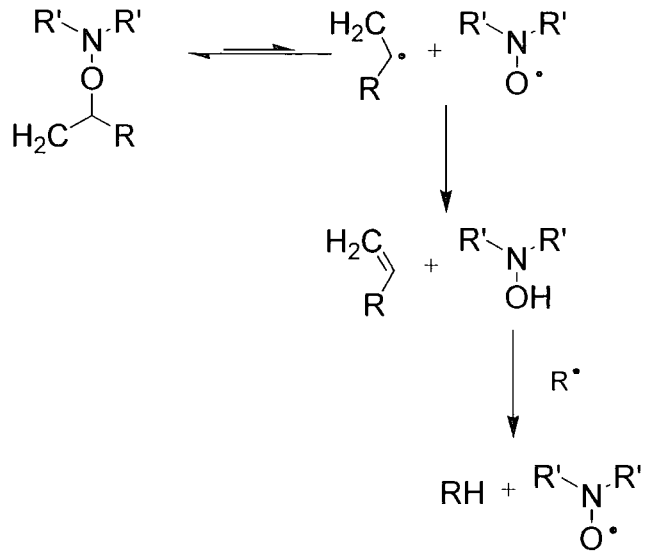

Figure 148 Catalytic termination of propagating radicals through hydroxylamine formation

Li *et al.*[206] investigated the propensity towards hydrogen transfer disproportionation of the 2,2,6,6-tetramethyl-1(1-phenylethoxy)piperidine, S-TEMPO [Figure 149], alkoxyamine by HPLC and ^{1}H NMR in 1,2,4-trichlorobenzene, DMSO and toluene. This alkoxyamine was selected as a model of a polystyrene alkoxyamine chain end and has been extensively utilised by a number of groups as a unimolecular initiator for controlled radical polymerisation.

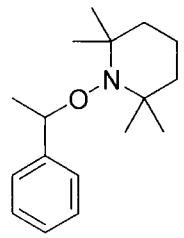

Figure 149 Styryl TEMPO alkoxyamine

[206] Li., I., Howell, B.A., Matyjaszewski, K., Shigemoto, T., Smith, P.B., Priddy, D.B., Macromolecules, **1995**, 28, 6692-6693

Heating of this alkoxyamine was shown to result in the formation of styrene, 2,3-divinyl butene and ethyl benzene. The ratios between decomposition reactions were shown to be temperature dependent and a reaction scheme was proposed of the form.

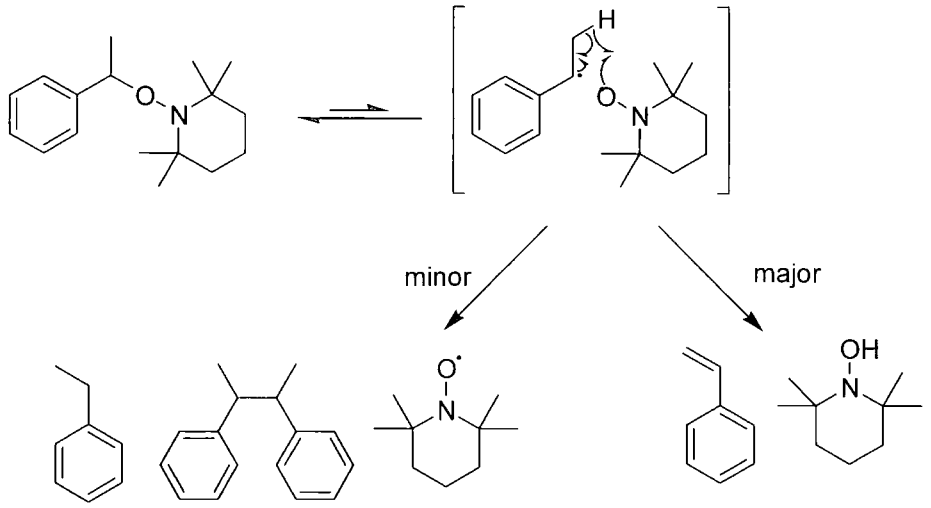

Figure 150 Li proposed reaction scheme for the homolysis of styryl TEMPO alkoxyamine

The results of this study suggest that in addition to combination termination hydrogen transfer disproportionation is likely to be a significant contributor to the formation of dead polymer chains and polydispersity broadening innitroxide mediated controlled radical polymerisation.

Fukuda *et al.*[207] investigated the decomposition under polymerisation conditions of the oligomeric and unimeric alkoxyamines, PS-TEMPO [Figure 151] and BS-TEMPO [Figure 152] in order to compare the decomposition of polymeric adduct to the unimolecular S-TEMPO species previously investigated by Li *et al.* on S-TEMPO.

[207] Ohno, K., Tsujii, Y., Fukuda, T., Macromolecules, **1997**, 30, 2503-2506

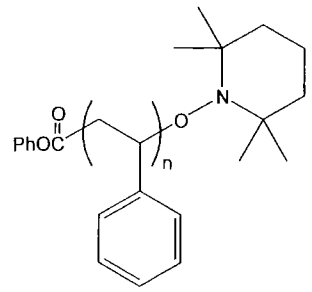

Figure 151 PS-TEMPO alkoxyamine

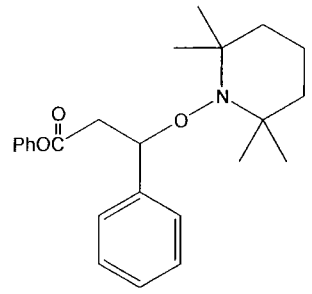

Figure 152 BS-TEMPO alkoxyamine

The level of hydrogen transfer disproportionation was observed to be significantly lower in both the BS-TEMPO and PS-TEMPO alkoxyamine adducts than that observed previously by Li *et al.* for styryl-TEMPO alkoxyamine. The reduction in rate of formation of disproportionation products was observed to be greater than that expected simply through the reduction in the number of available β-hydrogens from three to two. Although the rate of disproportion was reduced in comparison to that of the styryl alkoxyamine, it was still observed to occur to a significant extent. Heating of a sample for ten hours at temperatures comparable to those of polymerisation a 10% decomposition of chain ends was observed.

Skene *et al.*[208] studied an alkoxyamine analogous to a polystyrene chain end containing the penultimate chain end group [Figure 153] in order to improve initiator efficiency and provide an alternative chain end model to the S-TEMPO species used by a number of groups.

[208] Skene, W.G., Scaiano, J.C., Yap, G.P.A., Macromolecules, **2000**, 33, 3536-3542

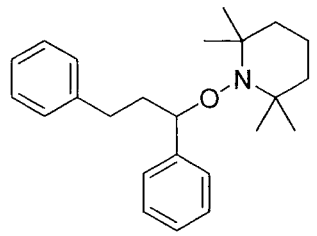

Figure 153 penultimate chain end TEMPO alkoxyamine

Skene *et al.* observed that at 125°C an one in thirty activation and deactivation cycles for the styryl TEMPO alkoxyamine studied by Li *et al.* results in hydrogen transfer disproportionation. In comparison no disproportionation was observed with the initiating species containing the penultimate styrene unit.

Goto *et al.*[209] determined the rates of disproportionation for several alkoxyamines based on TEMPO, HTEMPO, DBN and DEPN nitroxides by ^{1}H NMR spectroscopy in degassed d_8-toluene solution. These results showed a significant influence of nitroxide structure in determining the rate of hydrogen transfer disproportionation with the reduction in rate with increasing steric bulk of the nitroxide. In a similar result to that of Fukuda *et al.* the reactivity of PS-TEMPO alkoxyamine towards hydrogen transfer disproportionation compared to the styryl TEMPO analogue is greater than can be ascribed to the reduction in number of β-hydrogens. It was suggested that substitution at the β-alkoxyamine position results in adoption of an unfavourable conformation for disproportionation. It was noted that while the rates of activation for HTEMPO and TEMPO are similar, HTEMPO has a significantly lower rate of disproportionation and it was suggested that intramolecular hydrogen bonding in the nitroxide leads to the constraint of the nitroxide in an unfavourable conformation for the disproportionation reaction. Contrary to a suggestion from

[209] Goto, A., Kwak, Y., Yoshikawa, C., Tsujii, Y., Sugiura, Y., Fukuda, T., Macromolecules, **2002**, 35, 3520-3525

Scaiano that alkoxyamine hydrogen transfer decomposition occurs via a concerted mechanism, Goto *et al.* in examination of the rate of hydrogen transfer disproportionation in the presence of oxygen as an alkyl radical trap, observed a dramatic reduction in the rate of disproportionation. The authors interpreted this result as suggesting that the majority of disproportionation results from radical combination rather than radicals generated within a solvent cage or via a concerted mechanism. The hydrogen transfer disproportionation was shown to be far more significant in an alkoxyamine analogous to a methacrylate chain end terminated by TEMPO nitroxide than that of the comparable styryl species. Similarly methacrylate monomers were also shown by Fischer *et al.*[210] to be significantly more labile to hydrogen transfer disproportionation than styrene.

The effect of hydroxylamine formation and catalytic chain termination on kinetics and molecular weight distribution in controlled radical polymerisation were studied by Li *et al.* through Monte Carlo simulation. The incorporation of kinetic equations describing hydrogen transfer reactions into calculations resulted in a reduction in predicted polymerisation rate and a cessation of the polymerisation below complete conversion. The kinetic features predicted were compared to those observed in polymerisations of styrene and (meth)acrylate monomers and shown to match qualitatively with experiment. As in styrene, with autoinitiation the system is predicted to polymerise smoothly with a decrease in polydispersity index with conversion while in the absence of autoinitiation, as in TEMPO mediated (meth)acrylate polymerisation the polymerisation is predicted to cease at low conversion with the polydispersity passing through a minima before increasing with

[210] Ananchenko, G.S., Fischer, H., Journal of Polymer Science Part A: Polymer Chemistry, **2001**, 39, 3604-3621

conversion. It was concluded that hydrogen transfer disproportionation and chain termination by reduction of the propagating radical with hydroxylamine resulting in reduction of the rate of polymerisation and a broadening of the product polydispersity. It was suggested that the increased propensity of (meth)acrylates towards hydrogen transfer and the absence of autoinitiation contribute to the difficulties in polymerising these monomers. Further analyses of the polymerisation kinetics in systems with hydrogen transfer have been carried out by Souaille and Fischer which support the observations of Li *et al.*

In an attempt to rationalise the differing activities in polymerisation of styrene and butyl acrylate of the related alkoxyamines **11**, **6**, **12** and **8** in nitroxide mediated polymerisation we examined the propensity of each to undergo hydrogen abstraction to generate a vinyl unsaturated species and hydroxylamine by NMR spectroscopy in deuterated toluene.

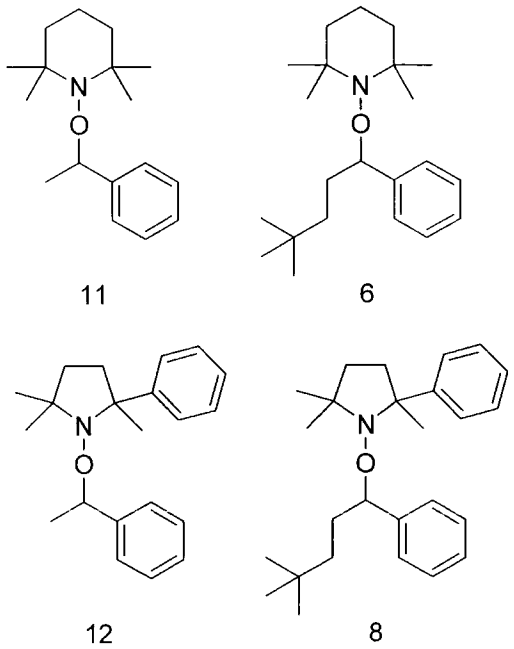

Figure 154 Alkoxyamines 6, 8, 11 and 12

Alkoxyamine **8** has previously been demonstrated in chapters 3 and 4 to improve the rate of styrene polymerisation compared to **6** and to be capable of initiating the

polymerisation of acrylates to high conversion, while the corresponding alkoxyamine **12** was less effective in styrene polymerisation and did not initiate acrylate polymerisation. As comparison the analogous alkoxyamines based on TEMPO were also examined.

Experimental

0.01Molar solutions of the alkoxyamines under study were prepared in d_8 toluene and placed in an NMR tube with a sealable fitting which could be fitted to a vacuum and nitrogen manifold. The sample was degassed by three consecutive freeze/pump/thaw cycles and backflushed with nitrogen. The sample tube was then immersed in a heated oil bath at 125°C and removed and spectra collected at regular intervals.

Results and Discussion

Heating of alkoxyamine **11** at 125°C resulted in formation of styrene as measured by comparison of the vinyl and alkoxyamine integrals in proton NMR at a rate in agreement with work published by Li *et al.* Heating of alkoxyamine **6** over a long period showed only low levels of vinyl species formation which were too low to obtain reliable integrals.

Alkoxyamines **12** and **8** based on the 2,2',5-trimethyl-5'-phenyl pyrrolidine-N-oxide nitroxide both showed minimal formation of unsaturated species over long spells of heating.

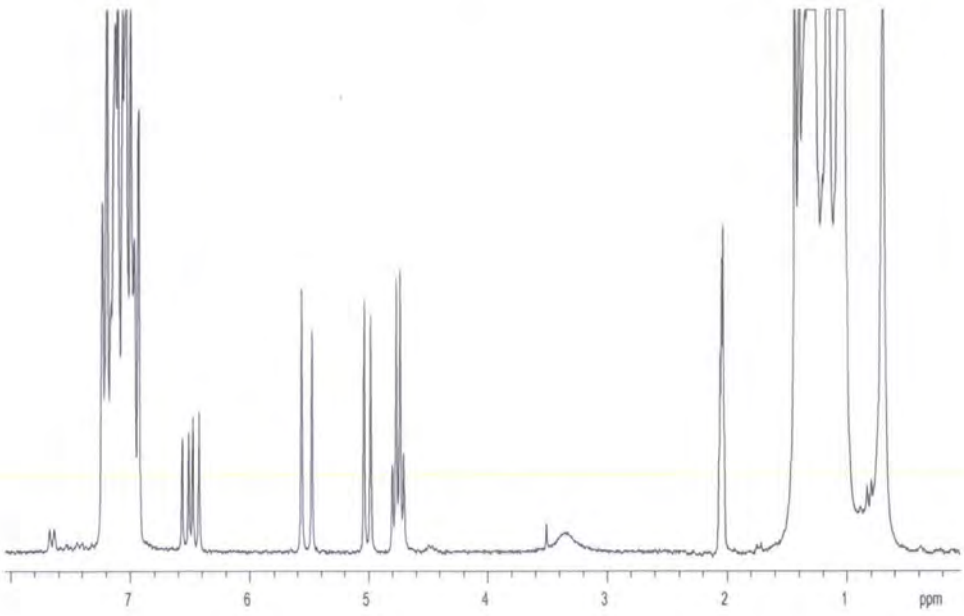

Figure 155 ^{1}H NMR spectra of alkoxyamine 11 after 8 hours of heating

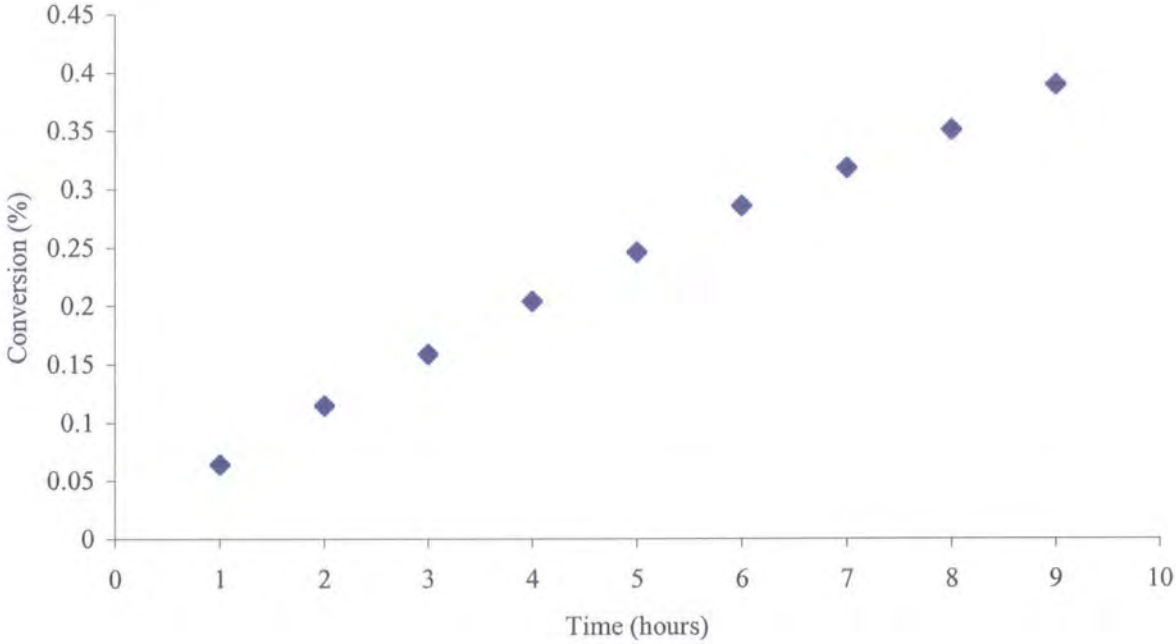

Figure 156 Fractional conversion of alkoxyamine 11 into styrene over 8 hours

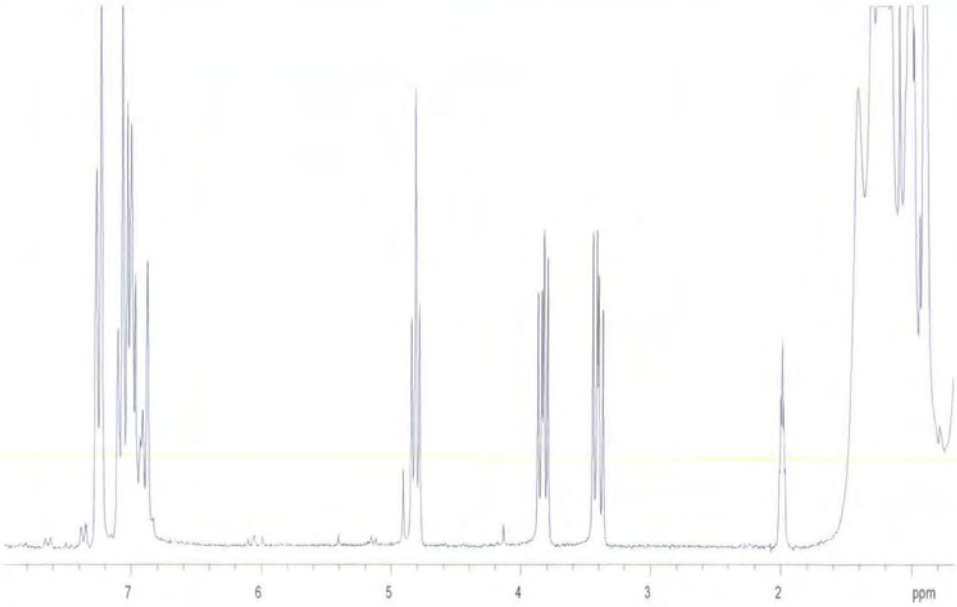

Figure 157 ^{1}H NMR spectra of alkoxyamine 6 after heating for 16 hours

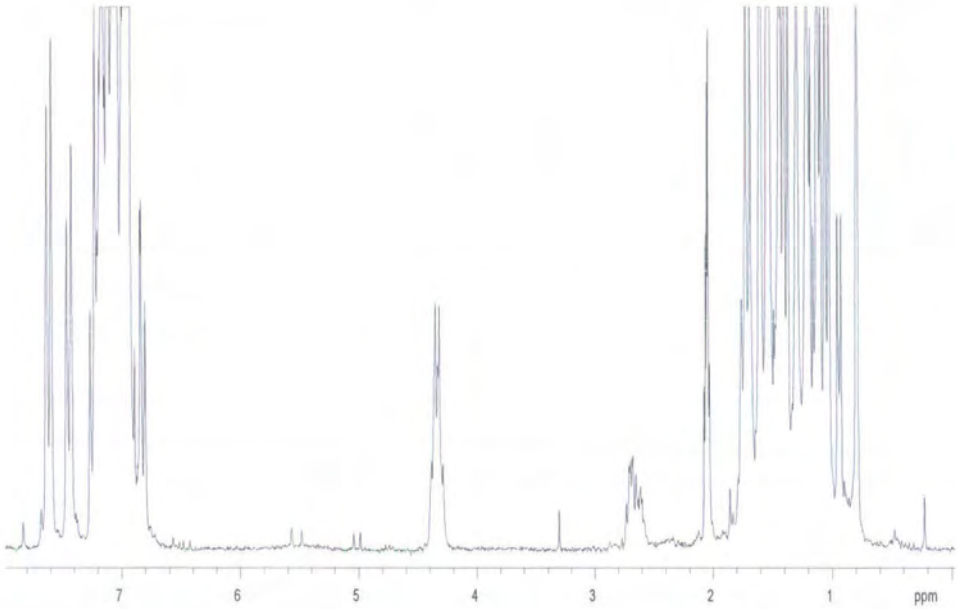

Figure 158 ^{1}H NMR spectra of alkoxyamine 12 after heating for 16 hours

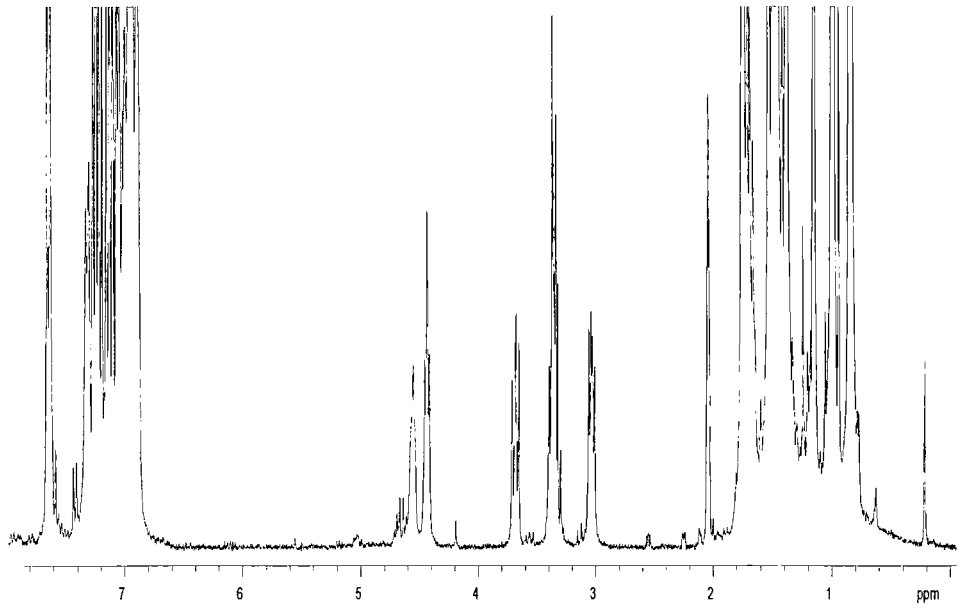

Figure 159 ^{1}H NMR spectra of alkoxyamine 8 after heating for 16 hours

These results suggest that the substitution of the styryl residue with a *tert*-butoxy group results in a reduction in the level of hydrogen transfer disproportionation and is likely to significantly improve initiator efficiency over the styryl alkoxyamine. This is in agreement with work presented by other groups showing that substitution at the beta position of the initiating fragment results in greatly reduced level of hydrogen transfer disproportionation. The low levels of decomposition even with the styryl fragment in alkoxyamines from 2,2,5-trimethyl-5-phenyl pyrrolidine-N-oxide nitroxide suggest that this nitroxide is less sterically or electronically less liable to undergoing the decomposition process.

Summary

Measurement of the rates of styrene formation from heating of alkoxyamine solutions resulted in the observation of structural influence of both nitroxide and alkyl fragment structure on this reaction. This is likely to positively impact the nitroxide mediated polymerisation performance of nitroxide **2** is a direct

consequence of it's lower propensity towards the hydrogen abstraction decomposition and that optimisation of initiator fragment and nitroxide to minimise the levels of this decomposition is central to control over polymerisation. The unimolecular approach to polymerisation relies on the stoichiometric introduction of propagating and mediating radicals however the decomposition of initiator to vinyl unsaturated moiety and hydroxylamine to any significant degree interferes with this delicate balance. This becomes increasingly relevant when considering the polymerisation of monomers, such as acrylates, in which the backbone hydrogens are significantly more labile and have been shown to more readily undergo this type of decomposition.

Conclusions

Nitroxide mediated controlled radical polymerisation has been examined by a number of groups both in fundamental studies into the chemistry and kinetics of polymerisation and as a means of preparing tailored macromolecular architectures.

Numerous studies have investigated the influence of nitroxide steric bulk in determining the rates of nitroxide capping and alkoxyamine homolysis reactions and hence the equilibrium between capped and propagating radical chain ends. The steric bulk of mediating nitroxide has also been shown to be influence the propensity of chain ends towards hydrogen transfer disproportionation, which leads to chain termination and broadening of the polymer product polydispersity.

Alkoxyamine homolysis rates have been shown to increase with increasing steric bulk of nitroxide while capping rates are reduced. A number of studies have investigated nitroxides bulkier than the TEMPO nitroxide which formed the bulk of early work into nitroxide mediated controlled radical polymerisation. Within initial work utilising nitroxide mediated polymerisation the rate of polymerisation was shown to be determined by the rate of monomer autoinitiation. This was shown to be a result of the persistent radical effect in which an excess of mediating nitroxides radicals is built up in the early stages of polymerisation as propagating radicals are lost through termination. In the absence of a continuing source of propagating radicals the excess of mediating species prevents polymerisation from occurring at any appreciable rate. This results in the limitation of achievable polymerisation rate and the restriction of nitroxide mediated controlled radical polymerisation to those monomers in which a feed of radicals is maintained through autoinitiation to replace those lost through termination. The application of sterically bulky nitroxides with a

hydrogen substituent adjacent to the nitroxide functionality to control of polymerisation has however been shown to result in both increase in polymerisation rate and the polymerisation of monomers in which autoinitiation was absent.

The polarity and ability of solvents to participate in hydrogen bonding have been shown to influence both nitroxide capping and alkoxyamine homolysis reactions. This influence has been ascribed to a consequence of changes in the spin distribution on the nitroxide as has been observed in the effect of solvent polarity and hydrogen bonding nature on the ESR spectra of nitroxides. Similar changes in spin density on nitroxide have been observed in the ESR spectra of nitroxides with substituents differing in electronic nature adjacent to the nitroxide. The effects on polymerisation of changes in substituent electronic nature of nitroxide mediating species have, to date, not been explicitly determined. In order to determine the influence of nitroxide electronic structures on the effectiveness of nitroxides in mediation of controlled radical polymerisation a series of nitroxides 2,2,5,5-tetramethylpyrrolidine-N-oxyl **1**, 2,5,5-trimethyl-2-phenylpyrrolidine-N-oxyl **2**, 2,5,5-trimethyl-2-*para*-N,N-dimethylanilinepyrrolidine-N-oxyl **3** and 2,5,5-trimethyl-2-*para*-trifluoromethylphenylpyrrolidine-N-oxyl **4** were prepared based on the five membered pyrrolidine-N-oxyl, PROXYL, nitroxide backbone. These nitroxides differed by replacement of a methyl group of 2,2,5,5-tetramethylpyrrolidine-N-oxyl nitroxide with aryl substituents of varying electronic structure. Nitroxides were prepared via a straightforward synthetic route in which suitable groups are added to a nitrone precursor as Grignard reagents to produce a hydroxylamine which was then oxidised under mild conditions to generate the desired nitroxide which was then purified by column chromatography.

These nitroxides have been previously investigated in mediating polymerisation of styrene with the in-situ formation of alkoxyamine unimolecular initiators. The associated alkoxyamines were prepared by mixing the di-*tert*-butyl peroxalate initiator with styrene and the appropriate nitroxide and heating to 40°C. Alkoxyamine was formed through the trapping by nitroxide of the radical from addition of a *tert*-butoxy radical to styrene. Polymerisation was subsequently initiated by the heating of the resulting reaction mixture to 125°C. This study showed differing rates of styrene polymerisation with the polymerisation mediated by nitroxide **1** as a middle case with nitroxide **3** mediated polymerisation significantly slower with a long induction period after which conversion began to increase and nitroxides **2** and **4** mediating polymerisation somewhat faster. The polymerisations mediated by all nitroxides **1-4** were observed to have linear increases in molecular weight with conversion with product polydispersities obtained between 1.64 and 1.16.

In order to remove any ambiguity in interpretation of this work through poorly defined initiating species it was decided to investigate these nitroxides as mediating species in polymerisation initiated by presynthesised and well-characterised alkoxyamine unimolecular initiators. These were prepared through a synthetic route similar to that of in-situ generation of alkoxyamine but rather than heating to initiate polymerisation these were isolated by column chromatography and stored in a freezer prior to use.

The electronic structure of the nitroxide was observed to have a marked influence on the rates of polymerisation of styrene and macromolecular control. A comparable rate to that of TEMPO based alkoxyamine and autoinitiation was observed for the alkoxyamines based on nitroxides **1** and **3** and significantly faster rates for

alkoxyamines based on nitroxides **2** and **4**. The results of gel permeation chromatography suggest that all polymerisations proceeded in a controlled fashion with a reduction in polydispersity with conversion to final product polydispersities between 1.25 and 1.5. Comparison of alkoxyamine initiated polymerisation mediated by nitroxides **2**, **3** and **4** bearing aryl substituents resulted in the observation that nitroxide **2** with a phenyl group adjacent to the nitroxide functionality mediated the polymerisation of styrene faster then TEMPO nitroxide while nitroxide **4** bearing an electron donating substituent N,N-dimethylamino group at the *ortho* position on the phenyl ring mediated polymerisation at a similar rate to TEMPO. The polymerisation mediated by the nitroxide **3** bearing an electron withdrawing trifluoromethyl group at the *ortho* position of the phenyl ring proceeded at a similar rate to nitroxide **2** but with a substantial deviation in molecular weight from theoretical predictions indicating poorer control over the polymerisation. These observations suggest that the effectiveness of nitroxides in mediating polymerisation is markedly influenced by the nitroxide electronic structure.

Experiments were carried out into the polymerisation rate influence of initiating alkoxyamine adduct concentration in order to assess whether the kinetic scheme applicable is that determined by the persistent radical effect or whether the Fischer derived kinetic model applies. No influence of alkoxyamine concentration on polymerisation rate was observed suggesting that the applicable kinetic scheme is that determined by the persistent radical effect.

As a result of the observed increased rate of styrene polymerisation mediated by nitroxide **2** over TEMPO with of with good control over polydispersity the effectiveness of this nitroxide in mediation of *n*-butyl acrylate was investigated. Polymerisation of this monomer with nitroxide mediation has proven historically

problematic because there is is little autoinitiation to generate propagating radicals to replace those lost through termination. Use of an alkoxyamine unimolecular initiator based on the TEMPO nitroxide **5** resulted in little conversion however the use of alkoxyamine based on nitroxide **2** resulted in very rapid polymerisation although gel permeation chromatography indicated that macromolecular control was limited. Addition of a small excess of nitroxide resulted in a reduced rate although macromolecular control was still poor with an increase in polydispersity with conversion. This was investigated through experiments measuring branch content through transfer to backbone using quantitative carbon NMR. The living nature of polymer prepared by mediation with this nitroxide was demonstrated through the preparation of a block copolymer through polymerisation of styrene initiated by poly(*n*-butyl acrylate). This would suggest that the alkoxyamine bond homolysis/capping reactions are outwith the kinetic limits described by Fischer resulting in a living but uncontrolled polymerisation.

Investigation into the reasons behind the improved activity of nitroxide **2** over TEMPO was carried out using ESR spectroscopy on alkoxyamines to investigate alkoxyamine bond homolysis in the presence of dissolved oxygen to trap alkyl radicals and maintain irreversible conditions. This study showed that the increased steric bulk of nitroxide **2** increases the rate of homolysis relative to that of the solely alkoxyamine based on nitroxide **1**. This is however comparable to the TEMPO nitroxide which although only bearing methyl groups adjacent to the nitroxide functionality is more steric bulk than the solely PROXYL nitroxide as a result of the difference in ring size raising questions over the reasons behind differences in polymerisation activity of these alkoxyamines.

Investigation of heated degassed alkoxyamine solutions by proton NMR in order to follow the formation of unsaturated products of hydrogen transfer disproportionation however suggests that phenyl PROXYL nitroxide has a substantially reduced propensity towards this reaction. This results in a reduced level of termination in polymerisations and the ability to polymerise acrylate monomer in which this termination process is thought to be more significant due to the presence of labile hydrogens on the backbone.

In addition the alkoxyamine alkyl fragment has been observed to have a large influence on the rate of alkoxyamine homolysis and hydrogen transfer disproportionation. This suggest that a number of alkoxyamines prepared from novel nitroxides previously investigated within the published literature might prove more effective in polymerisation with more suitably selected alkyl fragments.

It is therefore argued that in addition to steric influence on capping/homolysis equilibrium the electronic nature of nitroxides has a substantial influence on the effectiveness of nitroxide in polymerisation. Investigation into the utility of aryl PROXYL nitroxides results in the further conclusion that in addition to capping and homolysis rates the utility of nitroxide in controlled radical polymerisation is directly related to the propensity of nitroxides and the alkoxyamines prepared from them towards hydrogen transfer disproportionation.

Appendix - Crystallographic assignment

Empirical formula	C21 H35 N O2	
Formula weight	333.50	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	*Pbca* (No. 61)	
Unit cell dimensions	a = 15.532(4) Å	α= 90°
	b = 11.119(3) Å	β= 90°
	c = 23.247(5) Å	γ = 90°
Volume	4014.8(17) $Å^3$	
Density (calculated)	1.104 g/cm^3	
Absorption coefficient	0.069 mm^{-1}	
F(000)	1472	
Crystal size	1.00 × 0.66 × 0.14 mm^3	
θ range for data collection	1.75 to 32.5°.	
Index ranges	$-23 \leq h \leq 23, -16 \leq k \leq 16, -34 \leq l \leq 35$	
Reflections collected	60196	
Independent reflections	7229 [R(int) = 0.0195]	
Reflections with $I>2\sigma(I)$	6298	
Completeness to θ = 32.5°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.0000 and 0.8787	
Refinement method	Full-matrix least-squares on F^2	

Data / restraints / parameters	7229 / 0 / 251
Largest final shift/e.s.d. ratio	0.001
Goodness-of-fit on F^2	1.064
Final R indices [$I>2\sigma(I)$]	R1 = 0.0389, wR2 = 0.1064
R indices (all data)	R1 = 0.0451, wR2 = 0.1144
Largest diff. peak and hole	0.522 and -0.171 e.$Å^{-3}$

Atomic coordinates ($\times 10^5$) and equivalent isotropic displacement parameters ($Å^2$ $\times 10^4$). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	50726(3)	34047(4)	41290(2)	153(1)
O(2)	33509(3)	38797(5)	37666(2)	193(1)
N	56521(4)	25032(5)	38875(2)	160(1)
C(1)	43261(4)	28730(6)	43963(3)	155(1)
C(2)	55469(5)	25419(7)	32449(3)	212(1)
C(3)	62458(6)	17267(8)	29828(4)	320(2)
C(4)	71538(6)	20006(9)	31880(4)	328(2)
C(5)	71683(5)	19182(7)	38386(4)	263(2)
C(6)	65274(4)	27758(6)	41254(3)	184(1)
C(7)	55652(6)	38093(8)	29805(3)	286(2)
C(8)	46745(5)	19737(8)	30943(3)	274(2)
C(9)	68364(5)	40811(7)	40643(4)	243(1)
C(10)	65061(5)	24755(8)	47666(3)	272(2)
C(11)	44530(4)	25205(6)	50208(3)	157(1)
C(12)	43806(4)	13184(6)	51850(3)	192(1)
C(13)	44677(5)	9773(7)	57597(3)	242(1)
C(14)	46198(5)	18453(8)	61768(3)	257(2)
C(15)	46920(5)	30477(7)	60196(3)	232(1)
C(16)	46121(4)	33830(6)	54450(3)	191(1)

C(17)	36194(4)	38169(6)	43478(3)	185(1)
C(18)	26850(4)	47410(6)	36304(3)	185(1)
C(19)	18898(5)	45399(8)	40020(4)	298(2)
C(20)	24793(6)	44747(8)	30046(3)	278(2)
C(21)	30130(6)	60218(7)	36949(4)	320(2)

Bond lengths [Å] and angles [°].

O(1)-C(1)	1.4422(8)
O(1)-N	1.4595(7)
O(2)-C(17)	1.4158(8)
O(2)-C(18)	1.4446(8)
N-C(6)	1.4987(9)
N-C(2)	1.5033(9)
C(1)-C(11)	1.5168(9)
C(1)-C(17)	1.5228(9)
C(2)-C(8)	1.5354(11)
C(2)-C(7)	1.5377(12)
C(2)-C(3)	1.5399(11)
C(3)-C(4)	1.5198(14)
C(4)-C(5)	1.5153(13)
C(5)-C(6)	1.5312(10)
C(6)-C(10)	1.5280(10)
C(6)-C(9)	1.5353(11)
C(11)-C(12)	1.3945(10)
C(11)-C(16)	1.3975(9)
C(12)-C(13)	1.3955(10)
C(13)-C(14)	1.3883(12)
C(14)-C(15)	1.3906(12)
C(15)-C(16)	1.3924(10)

C(18)-C(20)	1.5187(10)
C(18)-C(21)	1.5200(11)
C(18)-C(19)	1.5238(11)

C(1)-O(1)-N	112.33(5)	C(12)-C(11)-C(1)	119.94(6)
C(17)-O(2)-C(18)	116.92(5)	C(16)-C(11)-C(1)	121.40(6)
O(1)-N-C(6)	106.17(5)	C(11)-C(12)-C(13)	120.97(7)
O(1)-N-C(2)	107.19(5)	C(14)-C(13)-C(12)	119.75(7)
C(6)-N-C(2)	117.35(5)	C(13)-C(14)-C(15)	119.90(7)
O(1)-C(1)-C(11)	114.45(5)	C(14)-C(15)-C(16)	120.16(7)
O(1)-C(1)-C(17)	105.37(5)	C(15)-C(16)-C(11)	120.59(7)
C(11)-C(1)-C(17)	110.04(5)	O(2)-C(17)-C(1)	108.48(5)
N-C(2)-C(8)	108.10(5)	O(2)-C(18)-C(20)	103.38(6)
N-C(2)-C(7)	114.93(6)	O(2)-C(18)-C(21)	111.07(6)
C(8)-C(2)-C(7)	107.59(7)	C(20)-C(18)-C(21)	110.35(6)
N-C(2)-C(3)	107.44(6)	O(2)-C(18)-C(19)	111.02(6)
C(8)-C(2)-C(3)	106.83(6)	C(20)-C(18)-C(19)	110.12(7)
C(7)-C(2)-C(3)	111.61(6)	C(21)-C(18)-C(19)	110.68(7)
C(4)-C(3)-C(2)	114.33(7)		
C(5)-C(4)-C(3)	108.36(7)		
C(4)-C(5)-C(6)	112.78(6)		
N-C(6)-C(10)	107.23(5)		
N-C(6)-C(5)	107.65(6)		
C(10)-C(6)-C(5)	107.62(6)		
N-C(6)-C(9)	116.15(5)		
C(10)-C(6)-C(9)	107.67(6)		
C(5)-C(6)-C(9)	110.19(6)		
C(12)-C(11)-C(16)	118.62(6)		

Anisotropic displacement parameters ($Å^2 \times 10^4$). The anisotropic displacement factor exponent takes the form: $-2\pi^2[\, h^2 a^{*2} U_{11} + \ldots + 2\, h\, k\, a^* b^* U_{12}\,]$

	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	141(2)	138(2)	182(2)	0(2)	34(2)	9(2)
O(2)	180(2)	243(2)	155(2)	7(2)	-21(2)	45(2)
N	160(2)	153(2)	169(2)	-10(2)	32(2)	23(2)
C(1)	140(2)	174(3)	151(2)	11(2)	7(2)	-9(2)
C(2)	229(3)	245(3)	160(3)	-23(2)	43(2)	-10(2)
C(3)	312(4)	365(4)	283(4)	-114(3)	104(3)	17(3)
C(4)	266(4)	364(4)	352(4)	-58(3)	136(3)	43(3)
C(5)	201(3)	224(3)	365(4)	21(3)	73(3)	65(2)
C(6)	149(2)	178(3)	225(3)	26(2)	17(2)	18(2)
C(7)	322(4)	336(4)	199(3)	78(3)	16(3)	-27(3)
C(8)	280(3)	342(4)	200(3)	-77(3)	9(3)	-48(3)
C(9)	187(3)	198(3)	345(4)	-3(3)	3(3)	-17(2)
C(10)	185(3)	396(4)	235(3)	76(3)	-20(2)	32(3)
C(11)	140(2)	175(3)	155(2)	12(2)	6(2)	0(2)
C(12)	195(3)	183(3)	199(3)	25(2)	-12(2)	-9(2)
C(13)	243(3)	248(3)	235(3)	78(2)	-14(2)	1(3)
C(14)	249(3)	343(4)	177(3)	53(3)	-17(2)	30(3)
C(15)	228(3)	299(3)	169(3)	-24(2)	-19(2)	27(3)
C(16)	191(3)	200(3)	181(3)	-11(2)	1(2)	1(2)
C(17)	157(3)	247(3)	151(3)	11(2)	-2(2)	34(2)

C(18)	189(3)	184(3)	184(3)	26(2)	-27(2)	4(2)
C(19)	210(3)	351(4)	333(4)	111(3)	43(3)	90(3)
C(20)	322(4)	299(4)	214(3)	7(3)	-91(3)	24(3)
C(21)	422(5)	208(3)	332(4)	53(3)	-137(3)	-59(3)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2$ $\times 10^3$) for 01srv187.

	x	y	z	U(iso)
H(1)	4152	2145	4172	16(2)
H(31)	6109	880	3078	40(3)
H(32)	6228	1808	2559	44(3)
H(41)	7564	1415	3021	44(3)
H(42)	7326	2818	3064	38(3)
H(51)	7755	2106	3977	32(3)
H(52)	7032	1083	3955	35(3)
H(71)	5145(5)	4323(4)	3179(3)	39(1)
H(72)	5418(5)	3761(1)	2570(3)	39(1)
H(73)	6144(4)	4154(4)	3024(3)	39(1)
H(81)	4625(2)	1184(7)	3284(3)	38(2)
H(82)	4632(2)	1870(6)	2674(3)	38(2)
H(83)	4207(3)	2502(5)	3228(3)	38(2)
H(91)	7018(5)	4226(2)	3668(3)	41(2)
H(92)	7321(5)	4220(2)	4324(3)	41(2)
H(93)	6367(4)	4628(4)	4162(3)	41(2)
H(101)	6137(5)	3078(6)	4973(2)	38(2)
H(102)	7106(4)	2503(7)	4926(1)	38(2)
H(103)	6261(5)	1649(6)	4822(1)	38(2)
H(12)	4270	723	4901	25(3)

H(13)	4423	154	5865	33(3)
H(14)	4674	1618	6569	38(3)
H(15)	4796	3642	6305	36(3)
H(16)	4666	4205	5340	25(3)
H(171)	3127	3595	4596	24(2)
H(172)	3840	4609	4475	24(2)
H(191)	1726(3)	3670(7)	3991(3)	43(2)
H(192)	1403(4)	5037(6)	3852(2)	43(2)
H(193)	2019(2)	4780(7)	4408(3)	43(2)
H(201)	3015(4)	4557(6)	2768(2)	39(1)
H(202)	2035(4)	5057(6)	2863(1)	39(1)
H(203)	2252(5)	3634(6)	2970(1)	39(1)
H(211)	3145(5)	6183(3)	4105(3)	45(2)
H(212)	2565(4)	6593(4)	3560(3)	45(2)
H(213)	3542(5)	6126(2)	3461(3)	45(2)

Table 6. Torsion angles [°] for 01srv187.

C(1)-O(1)-N-C(6)	-128.03(5)
C(1)-O(1)-N-C(2)	105.78(6)
N-O(1)-C(1)-C(11)	86.82(6)
N-O(1)-C(1)-C(17)	-152.16(5)
O(1)-N-C(2)-C(8)	-72.99(7)
C(6)-N-C(2)-C(8)	167.78(6)
O(1)-N-C(2)-C(7)	47.18(7)
C(6)-N-C(2)-C(7)	-72.05(8)
O(1)-N-C(2)-C(3)	172.05(5)
C(6)-N-C(2)-C(3)	52.82(8)
N-C(2)-C(3)-C(4)	-52.39(9)
C(8)-C(2)-C(3)-C(4)	-168.19(7)
C(7)-C(2)-C(3)-C(4)	74.46(9)
C(2)-C(3)-C(4)-C(5)	56.39(10)
C(3)-C(4)-C(5)-C(6)	-57.99(9)
O(1)-N-C(6)-C(10)	69.52(6)
C(2)-N-C(6)-C(10)	-170.72(6)
O(1)-N-C(6)-C(5)	-174.94(5)
C(2)-N-C(6)-C(5)	-55.17(7)
O(1)-N-C(6)-C(9)	-50.91(7)
C(2)-N-C(6)-C(9)	68.86(8)
C(4)-C(5)-C(6)-N	56.34(8)
C(4)-C(5)-C(6)-C(10)	171.63(7)

C(4)-C(5)-C(6)-C(9)	-71.23(8)
O(1)-C(1)-C(11)-C(12)	-117.89(6)
C(17)-C(1)-C(11)-C(12)	123.70(7)
O(1)-C(1)-C(11)-C(16)	64.45(8)
C(17)-C(1)-C(11)-C(16)	-53.96(8)
C(18)-O(2)-C(17)-C(1)	-179.32(5)
O(1)-C(1)-C(17)-O(2)	72.26(6)
C(11)-C(1)-C(17)-O(2)	-163.88(5)
C(17)-O(2)-C(18)-C(20)	-173.50(6)
C(17)-O(2)-C(18)-C(21)	68.17(8)
C(17)-O(2)-C(18)-C(19)	-55.45(8)