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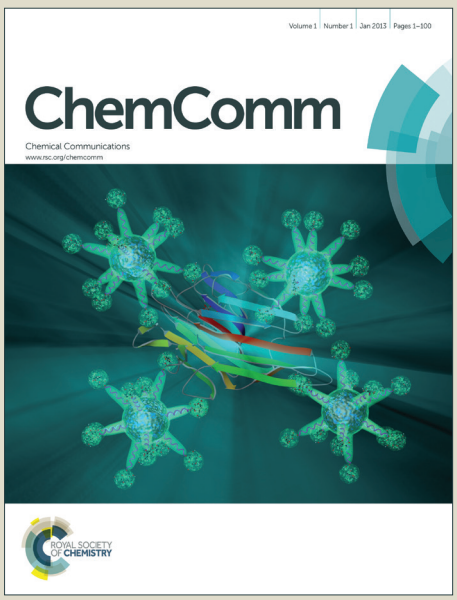

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ARTICLE TYPE

Labile Alkoxyamines: Past, Present, and Future

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Alkoxyamines - *per*-alkylated derivatives of hydroxylamine $R^1R^2NO—R^3$ - can undergo C—ON bond homolysis to release a persistent nitroxyl radical $R^1R^2NO•$ and a transient alkyl radical $R^3•$. Although they were considered as an oddity when discovered in 1974, their properties have been extensively studied since the seminal work of Solomon, Rizzardo and Cacioli (*Chem. Abstr.*, 102, 221335q), who patented the key role of alkoxyamines in nitroxide-mediated polymerization (NMP) in 1985. This *feature article* surveys and assesses the various applications of alkoxyamines: in tin-free radical chemistry, e.g., for the elaboration of carbo- or hetero-cycles, for the development of new reactions, for total synthesis of natural products; in polymerization under thermal conditions (NMP) or photochemical conditions (nitroxide-mediated photo-polymerization, NMP2); and in the design of smart materials. In this *feature article*, we also describe our recent findings concerning the chemical triggering of the C—ON bond homolysis in alkoxyamines, affording the controlled generation of alkyl radicals at room temperature. Based on these results, we describe herein some new opportunities for applications in the field of smart materials, and of course, some possible developments as new initiators for NMP as well as an entirely new field of application: the use of alkoxyamines as theranostic agents. Indeed, each of the radicals released after homolysis can play an appealing role: the nitroxide, through dynamic nuclear polarization (DNP), can be used for imagery purposes (diagnostic property), while the alkyl radical can be used to induce cellular disorders in abnormal cells (therapeutic activity).

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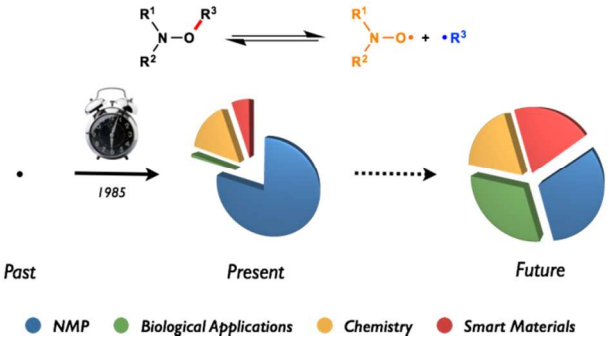


TOC

How the fields of application have changed during the last 40 years and the future perspectives.

Introduction

Alkoxyamines (trialkylhydroxylamines) have been known since the early 20th century[1] and their chemistry, either as reactants/products or intermediates, has been reviewed several times.[2-4] However, this family of molecules, especially the labile ones, was considered as seemingly trivial and of minor use until the 1990s,[5] when they started to be used as initiators for one of the most promising techniques for controlling radical polymerization:[6] Nitroxide Mediated Polymerization (NMP, vide infra).[7] In fact, the renewed interest in this family is only due to the radical reactivity displayed by some of its members. In this *feature article*, we propose to describe the major milestones, from the discovery of the radical reactivity of alkoxyamines to their implementation in industry,[8,9] and their potentially new

applications (Figure 1).

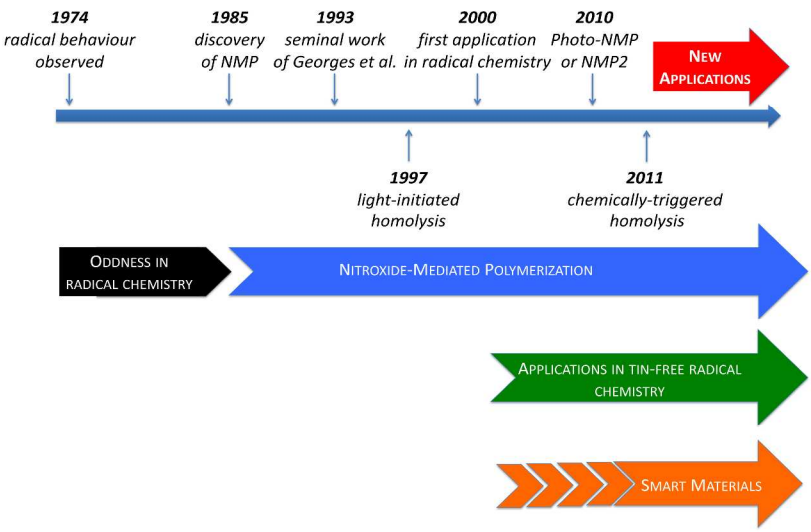
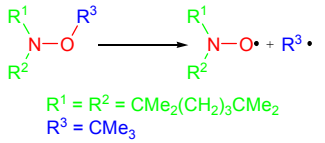


Figure 1. Alkoxyamines used as radical initiators: timescale and milestones

The discovery of the radical reactivity of alkoxyamines and of the Nitroxide Mediated Polymerization

Indeed, in 1974, for the first time Kovtun *et al.*[10] reported that the stability of alkoxyamines was unexpectedly dependent on experimental conditions.[¥,11] They observed that the decomposition of alkoxyamines into nitroxide and alkyl radicals (Scheme 1) was dramatically dependent on the presence and amount of scavengers such as oxygen or iodine. This chemistry did not arouse too much interest[12,13] for one decade, except for a few articles related to the degradation of polymers.[14-17] In fact, the kinetics underlying this amazing result were unveiled 24 years later by Fischer and coll.[18] Indeed, the apparent high stability of alkoxyamines is governed by the so-called *"Persistent Radical Effect"*.[19-21,þ] Using alkoxyamine **1** (Figure 2), Fischer and coll.[18] showed that it was completely decomposed in *ca.* 90 minutes at 80 °C when the experiment was performed in the presence of an alkyl radical scavenger (galvinoxyl) whereas only 2% was decomposed in *ca.* 10 hours in its absence!7



Scheme 1. Homolysis of the C—ON bond in alkoxyamines. An example of the lability of alkoxyamine - R^1 and R^2 for the nitroxyl fragment and R^3 as alkyl fragment - investigated in the presence of oxygen by Kovtun *et al.*[10]

In 1985, Solomon, Rizzardo, and Cacioli[22] patented the concept of Nitroxide Mediated Polymerization, which relies on the reversible homolysis of the C—ON bond of alkoxyamines (Scheme 2a,b).[23,24] They were the first[25] to improve the conventional 3-stage scheme for radical polymerization by proposing additional steps in each stage (Scheme 2b). This improved scheme is often displayed in its oversimplified form (Scheme 2c).[§,26] This major discovery did not arouse too much interest in the community of polymer chemists, until the seminal work of George and coll.[27,28] 8 years later (Scheme 2d). Using a bi-component system based on 2,2,6,6-tetramethylpiperidinyl-1-*N*-oxyl radical (TEMPO) and dibenzoylperoxide, they showed that the radical polymerization of styrene is nicely controlled, affording polymers exhibiting narrow polydispersity indices (< 1.5). Keeping the robustness of the radical polymerization, NMP now plays a major role in the preparation of well controlled and defined polymer structures.5-7,[26,29-35] Since then, it has triggered a tremendous amount of work in different fields, spanning from kinetics investigations,[29] design of new initiators,[36,37] preparation of new materials,[30] to industrial applications.[33] All the results reported in the cited reviews show that NMP is now a mature technique that is currently used in industry6 to prepare new polymers and new materials and this aspect will not be discussed any further.5,[6,33-34]

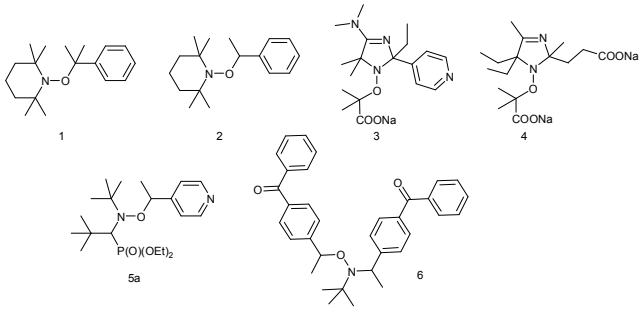


Figure 2. Some examples of alkoxyamines developed for new modes of initiation

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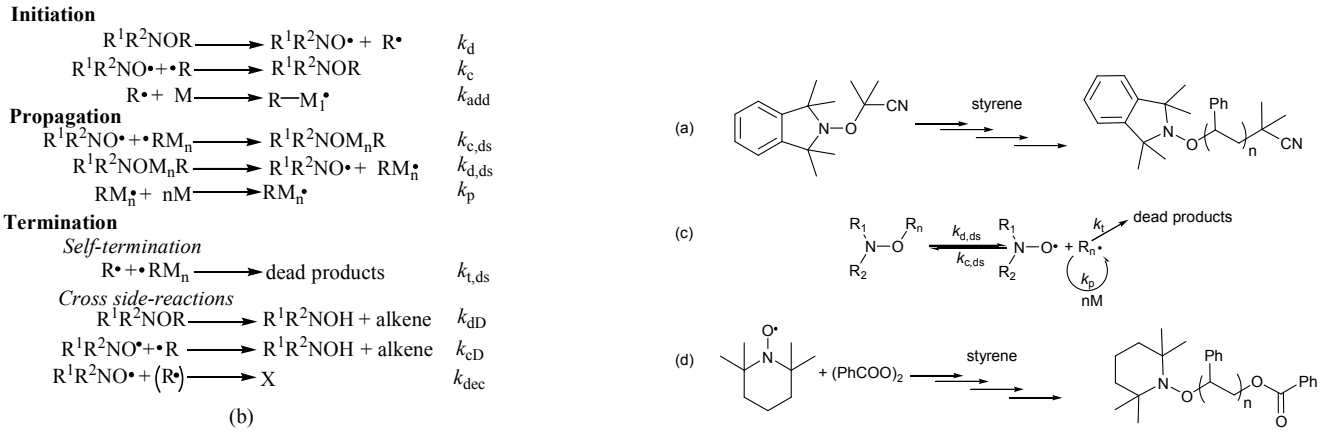


Scheme 2. (a) An example of the first NMP experiment proposed by Solomon et *al.*[22]; (b) complete kinetic scheme for NMP, and (c) its oversimplified scheme; and (d) bi-component system for NMP proposed by Georges et al.[27,28] For the experimental conditions in (a) and (d), see the references cited. k_d and k_c: C—ON bond homolysis and reformation rate constants of the initiator; $k_{d,ds}$ and $k_{c,ds}$: C—ON bond homolysis and reformation rate constants of the initiator and the macro-alkoxyamine (dormant species ds), respectively; k_{add}: rate constant for the addition of the initiating alkyl radical onto the monomer; k_p: propagation rate constant; $k_{t,ds}$: termination rate constants of the polymer radical (in general, a magnitude close to that of molecular species); k_{dD}: rate constant for the intramolecular proton transfer (IPT) in molecular and macromolecular alkoxyamines, k_{cD}: rate constant for the intermolecular hydrogen-atom transfer (HAT) between the nitroxide and the alkyl radical; k_{dec}: rate constant for the nitroxide degradation processes.

Fundamentals of the radical reactivity of alkoxyamines

During the last 20 years, the effects ruling C—ON bond homolysis and its reformation have been carefully and extensively studied. As these effects are not the topic of this article, they will be addressed briefly. The reformation of the alkoxyamine C—ON bond has been the purpose of a recent review whose the main lines are displayed in Figure 3.[38] Interestingly, the substituents of the alkyl radical and the nitroxide involve effects that are either additive or synergetic, except for the effect of the penultimate unit which is not yet clear. As expected, the main effects involved in ruling k_c are the stabilization, the bulkiness, and the polarity of both the alkyl radical and the nitroxide, each to a different extent depending on the species. The solvent effects were also reported in this review.

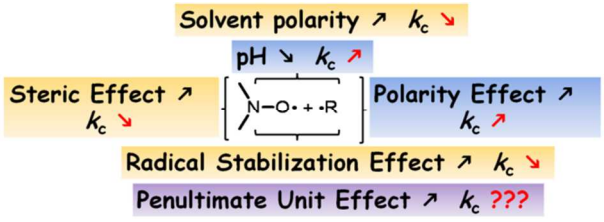


Figure 3. Effects ruling the reformation rate constant k_c. Reprinted with permission from E. G. Bagryaskaya, S. R. A. Marque, *Chem. Rev.,* 2014, ASAP. Copyright 2014 Americal Chemical Society.

The alkoxyamine C—ON bond homolysis, although shortly discussed in several reviews, has not yet been the topic of a devoted review.[5-7,21,29] The main effects are displayed in Figure 4 and briefly discussed. Interestingly, all the main effects of the R_3 group on k_d exhibit the same trend whereas, on the nitroxyl fragment R^1R^2NO, the steric and polar effects afford antagonistic trends. Moreover, when the whole structure is considered some synergetic antagonistic effects can arise. Furthermore, the impact of these effects can be strikingly modified by minor/side effects such as intramolecular hydrogen bonding, anomeric and anchimeric effects, long range effects etc.[7,26] Nevertheless, it has been possible to develop structure reactivity relationships (SRR) robust enough to predict either the right value of k_d or at least the trend expected.[39-41] Taking into account the versatility of the structures and the potential applications (vide infra), it is not possible to provide accurate and reliable rules on what the "*ideal*" or "*perfect*" structure is. Nevertheless, theoretical[42,43] and empirical[39-41] tools are available to determine k_d and k_c values, so that the success or the failure of the aimed application might be envisioned.

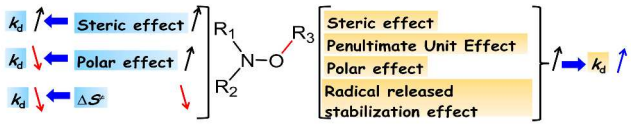
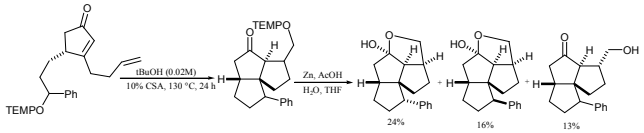


Figure 4. Main effects involved in the C—ON bond homolysis of alkoxyamines

Alkoxyamines for Tin-Free Radical Chemistry

In 2000, Studer[44] reported the first application of alkoxyamines as substitutes in tin-free radical chemistry, as highlighted by the preparation of triquinane via radical cascade cyclizations

(Scheme 3). Several applications have followed: the formation of lactones or lactames[45,46] via the Ueno-Stork reaction,[47,48] conjugative addition/cyclization/elimination,[49-51] intramolecular homolytic aromatic substitution,[51,52] 1,2-intermolecular radical addition,[50,53,54,] carboxyaminoxylation,[55] isonitrilation,[56]or metal free-carbonylation (Figure 5).[57] Theodorakis and coll.,[58] in their preparation of (-)-fusarisetin A (Scheme 4), highlighted the efficiency and the interest to use alkoxyamine as radical initiator.



Scheme 3. First example of an alkoxyamine used as initiator in Tin Free-radical Chemistry.

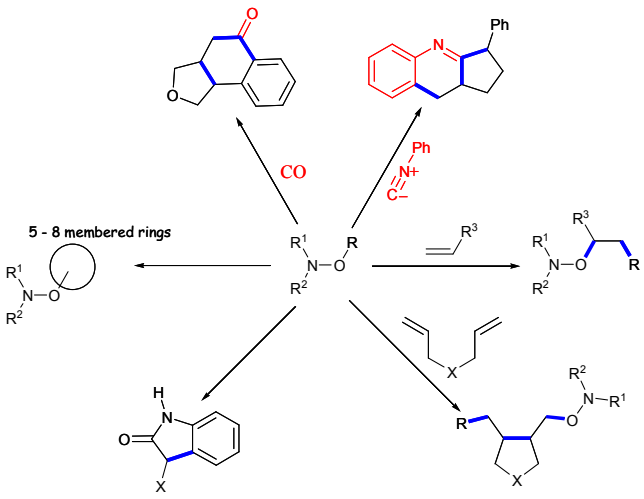
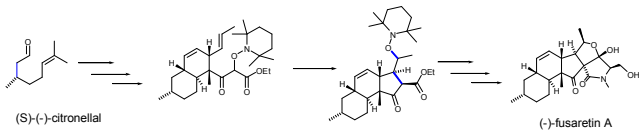


Figure 5. Various applications of alkoxyamines as synthetic tools (in blue, newly formed bonds; in red, new fragments added).



Scheme 4. Preparation of (-)-fusaretin A based on the radical cyclization (in blue, newly formed bonds) involving the use of an alkoxyamine as thermal radical initiator.

Photolysis of alkoxyamines and Photo-NMP

In 1997, Scaiano et al.[59] showed that laser-flash irradiation of alkoxyamines **1** and **2** (Figure 1) generates nitroxides and alkyl radicals through a homolytic process. It was a decade later[60-62] that NMP under irradiation (photo-NMP or NMP2, Figure 6) was developed simultaneously by Gigmes and coll.[63,64] and Yoshida et al.[65] Gigmes et al.[63] showed that the photo-labile alkoxyamine **6** was suitable for controlling the photo-polymerization of *n*-butyl acrylate, and developped nice applications in the preparation of covalently bonded multilayered micropatterns.[66]

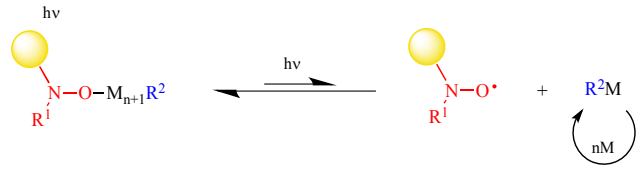


Figure 6. Principle of nitroxide-mediated photopolymerization (● as chromophore group). Copyrigth 2012 Wiley. Used with permission from D. Gigmes, S. R. A. Marque, Nitroxide Mediated Polymerization and its Applications. In *Encyclopedia of Radicals in Chemistry, Biology, and Materials*; C. Chatgilialoglu, A. Studer, Eds.; Wiley: Chichester, U.K., 2012, Vol. **4**, 1813-1850.

Chemical (de)activation of alkoxyamines

In 2009, the possible (de)activation of the alkoxyamine C—ON bond homolysis based on chemical changes on the nitroxyl fragment was suggested by Marx et al.,[67] and, independently, a striking effect of the protonation of the nitroxyl moiety on the decomposition pathways during ESI-MS experiments was reported by Mazarin et al.[68] However, the first kinetic evidence of the effect of protonation on the C—ON homolysis was only reported in 2011 by Brémond and Marque[69] who showed, in sharp contrast to the earlier observations,[70-73] that k_d values were strikingly increased upon protonation (**5b**) of the alkyl fragment of alkoxyamine **5a** (Scheme 5), as well as upon oxidation (**5c**), acylation (**5d**), alkylation (**5e,f**), and complexation (**5g**) of the pyridinyl moiety (Scheme 5),[74] as expected from structure reactivity relationships.[41] In the same year, Bagryanskaya and coll.[75] reported the reverse effect of the protonation for **3** and **4**, i.e., the strengthening of the alkoxyamine C—ON bond upon protonation of the nitroxyl fragment. Hence, a clear decrease in the homolysis rate constant k_d was observed from basic to acidic pH (Figure 7), as expected from the polar effect of the nitroxide fragment (Figure 4).[39,40] The activation/deactivation events were efficiently applied to NMP.[75,76]

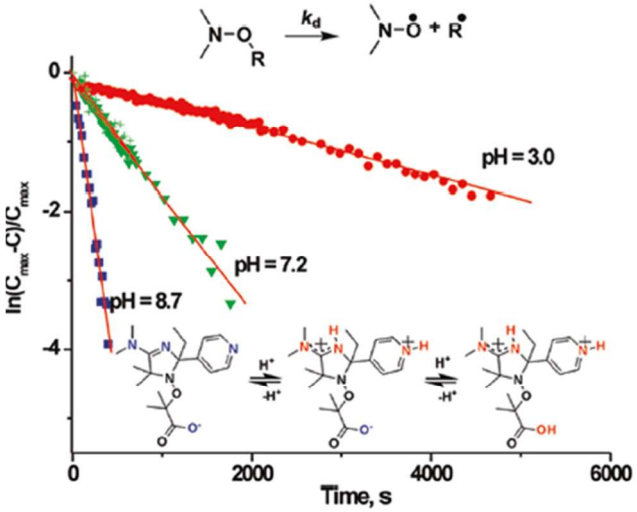
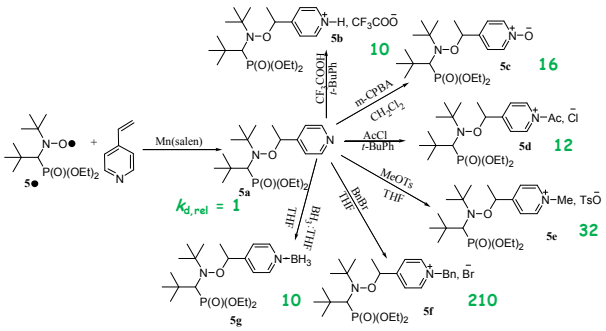


Figure 7. Effect of the protonation on k_d of **3**. (■) pH = 8.7, (▼) pH = 7.2 and (●) pH = 3.0. Reprinted with permission from M. V. Edeleva, I. A. Kirilyuk, I. F. Zhurko, D. A. Parkhomenko, Y. P. Tsentalovich, E. G. Bagryanskaya, *J. Org. Chem.*, 2011, **76**, 5558-5573. Copyright 2014 Americal Chemical Society.



Scheme 5. Different types of chemical activation for alkoxyamine **5a**. Green values are for $k_{d,rel} = k_{d,5b\text{-}5g}/k_{d,5a}$.

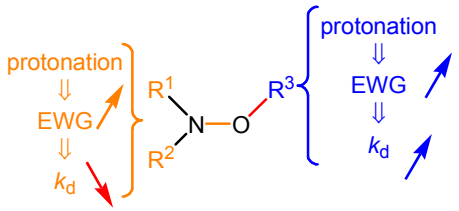


Figure 8. Consequences of the protonation depending on the site of protonation.

Consequently, the same mode of activation, i.e., protonation of an nitrogen atom, has an antagonistic effect on the alkoxyamine C—ON bond homolysis, whether the protonation occurs on the nitroxyl fragment or on the alkyl fragment. That is, upon protonation, the electron-withdrawing properties of the substituents are increased, leading either to a striking decrease in k_d for the nitroxyl moiety or to a dramatic increase in k_d for the alkyl fragment (Figure 8). This effect depends only on the increase/decrease in the electron withdrawing properties of the substituents,[39-41] implying a change in k_d, as displayed in Figure 8 and as highlighted with **5a** – **5g** and **3** in Scheme 5 and in Figure 7, respectively.

In fact, the chemical triggering of the C—ON bond homolysis led us to develop the concept of smart spin probes (doted red line in Figure 9). Indeed, alkoxyamines can be gathered in 3 families, depending on the strength of the C—ON bond (Bond Dissociation Energy, BDE): for BDE < 100 kJ/mol ($t_{1/2,\ 20\ °C}$ < 30 min.), a family of alkoxyamines that are too unstable to be handled and stored easily and safely, and that have been of *no use* up to now; for 100 kJ/mol < BDE < 140 kJ/mol, a family which comprises all alkoxyamines currently applied to NMP and radical chemistry; and for BDE > 140 kJ/mol ($t_{1/2,\ 20°\ C}$ > 800 years or $t_{1/2,\ 200°\ C}$ > 8 s),[IO] a family of alkoxyamines that are too stable to be involved in controlled radical reactions. In fact, the concept of smart spin probes relies on the activation of highly stable alkoxyamines into highly labile alkoxyamines (red dotted arrow in Figure 9) for new applications in biology and for smart materials. Our recent results nicely support this concept, as we observed a clear activation (green arrow in Figure 9). Thus our research is now focused on the development of very stable alkoxyamines that can be chemically or biologically switched to highly labile alkoxyamines (red dotted arrow in Figure 9). It has already been possible, by combining solvent effects and chemical activation, to develop alkoxyamine **5e** that exhibits $t_{1/2}$ = 48 min. at 37 °C in water,[77] which led us to envision some applications of alkoxyamines in some fields of biology such as theranostics.

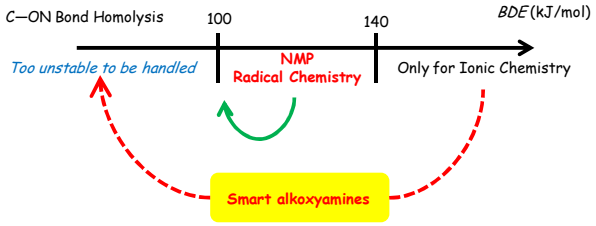


Figure 9. Smart spin probe concept. Reproduced from Ref. 79

Application of alkoxyamines as Theranostic agents

Ten years ago a new field emerged: Theranostics[Σ78] where concomitant therapeutic and diagnostic properties can be exhibited by a single molecule, which makes it possible to monitor in situ and directly the efficiency of drugs. Interestingly, alkoxyamines are able to release two different types of radicals: a rather persistent nitroxide (several minutes to several hours of life-time in biological conditions) and a transient, generally highly reactive, alkyl radical. Our recent results led us to propose the concept displayed in Figure 10 and an approach to the use of alkoxyamines as theranostic agents (Figure 11).[79]

When the decomposition of an alkoxyamine occurs *at the right time and at the right place* – rather quickly and in unhealthy cells – it generates alkyl radical and nitroxide, being each endorsed with a specific role. Alkyl radicals are highly reactive transient species that generate biological disorders[80] – by H-abstraction, addition onto unsaturated bonds, electron transfer, etc – which in turn trigger the cell death process[81] (necrosis and apoptosis). Hence, they exhibit therapeutic activity (Figure 10). Nitroxides are persistent radical species which can be detected readily or through the modifications they cause in the magnetic properties of their surroundings. They can be used to monitor the efficiency of the drug when using techniques such as Electron Paramagnetic Resonance Imaging (EPRI) or Overhauser-enhanced Magnetic Resonance Imaging (OMRI).[82,83] Hence, they exhibit a diagnostic property. This concept (Figure 10) will be successful only if the homolysis of the alkoxyamine is selectively triggered *at the right time*, *at the right place*, and with a rate high enough to ensure a nitroxide concentration suitable for monitoring.

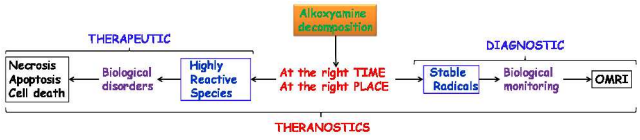


Figure 10. Theranostic concept based on the radical chemistry of alkoxyamines. Reproduced from Ref. 79.

To fulfill the requirements described above, a 3-fragment alkoxyamine should be designed (Figure 11): the activation/addressing fragment (green part), the virtual alkyl radical (yellow circle), and the virtual nitroxide (blue part). The triggering of the alkoxyamine homolysis can be performed either through chemical or physical activation combined to selective addressing or through a chemical reaction activated by the addressing event.[79] The activation will release a transient alkoxyamine (dotted frame Figure 11) that will decompose into a highly reactive radical[81] (red frame) – increasing the amount of reactive oxygen species (ROS)[81] or reacting with biomolecules – and into a persistent nitroxide (dark blue frame) which can be

used to monitor the biological process involved using OMRI.[82,83]

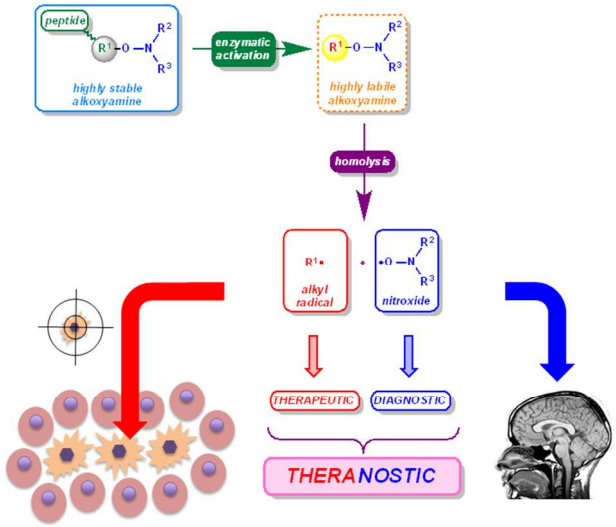


Figure 11. Theranostic concept applied to alkoxyamines.

Alkoxyamines for Smart Materials

For the past decade, alkoxyamines have been used in the development of smart materials. Indeed, the preliminary experiments performed by Otsuka et al.,[84] about 10 years ago, on the scrambling of polymer chains based on the homolysis of the alkoxyamine led Rong and coll.[85,86] to propose self-healing materials based on reversible alkoxyamine homolysis (Figure 12). Recently, Studer and coll.[87] showed that reversible homolysis can be applied to the development of dynamic microcrystal assemblies, as highlighted by the alternate green and red zeolithes in Figure 13. Such types of structure are opening new opportunities in photonics.

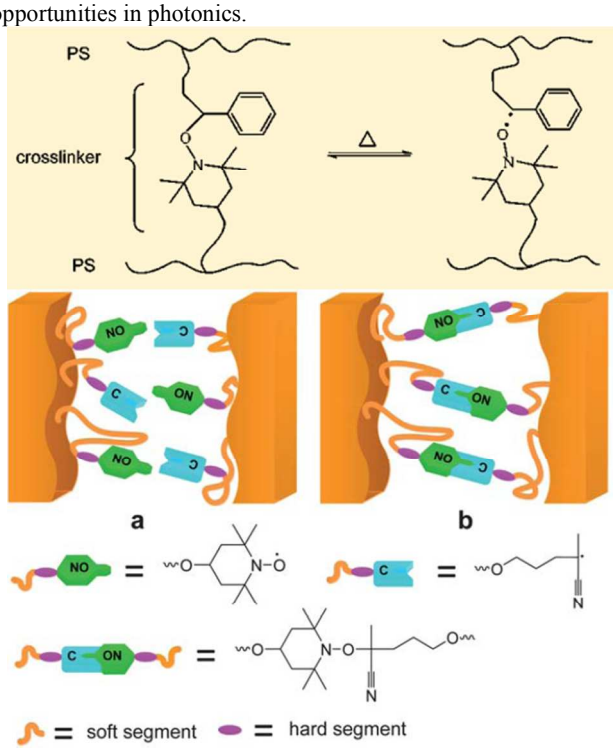


Figure 12. Self-healing polymer based on the reversible alkoxyamine homolysis. Top: Reprinted with permission from C. Yuan, M. Z. Rong, M. Q. Zhang, Z. P. Zhang, Y. C. Yuan, *Chem. Mater.,* 2011, **23**, 5076−5081. Copyright 2011 Americal Chemical Society. Bottom: Reproduced from Ref. 86.

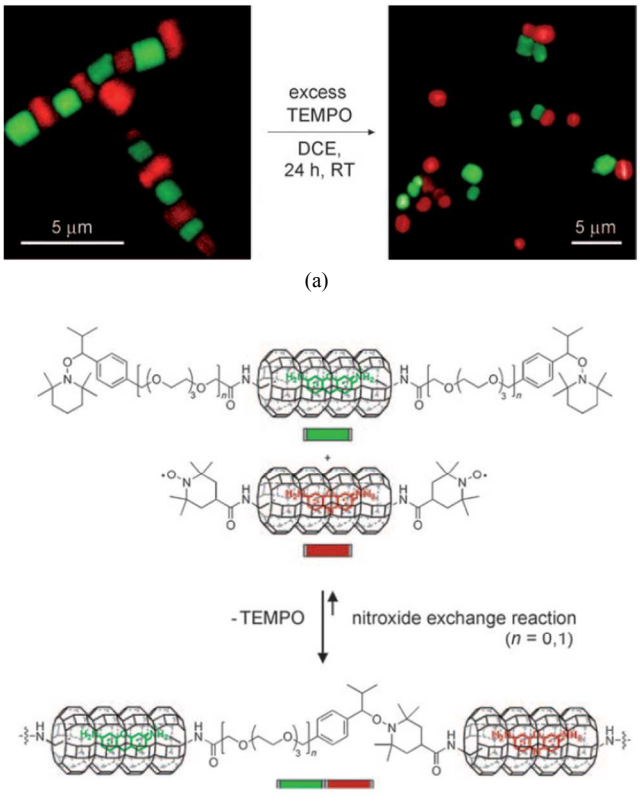


Figure 13. (a) Confocal microscopy images showing the reversibility of the chain formation with zeolites. (b) Nitroxide exchange reaction of alkoxyamine functionalized zeolite L crystal (green zeolites) with nitroxide-modified (red zeolites) to form ordered zeolite chains. Copyrigth 2010 Wiley. Used with permission from B. Schulte, M. Tsotsalas, M. Becker, A. Studer, L. De Cola, *Angew. Chem. Int. Ed.,* 2010, **49**, 6881-6884.

However, up to now, all applications have relied on a change in temperature and so for each application a specific alkoxyamine must be designed. Chemical triggering and biological triggering will lead to the development of new materials with innovative self-healing or optoelectronic properties. One can imagine C—ON homolysis controlled by chemical or biological stimuli allowing the modulation of channel accessibility, of the permeability of materials, and of the magnetic properties of materials, everything being performed from room to physiological temperature. For example, the reversible homolysis of an alkoxyamine C—ON bond triggered by a change in pH has the potential to be applied to the control of access to channels in membranes, as highlighted in Figure 14.

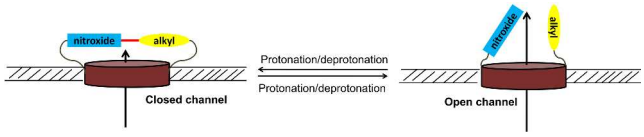


Figure 14. Model for controlling the passage of a solvent through the channels of a membrane.

Conclusion

Thirty years after the discovery of NMP, labile alkoxyamines can be considered as valuable initiators for radical reactions. Indeed, they are currently used in industry to prepare tailored polymers by NMP, just as peroxides and homologues are used to prepare basic/standard polymers by radical polymerization (Figure 15).[5,6,8,9,31] It is clear that alkoxyamines can now be considered as conventional reactants for radical chemistry in industry. Nevertheless, chemically triggered C—ON bond homolysis is opening new perspectives for NMP: *i*) new initiators complying with the REACH directives, i.e. easier to store, to handle, to ship and much less hazardous than conventional thermal initiators;[88] and *ii*) new initiator for surface polymerizations on inorganic core particles which would be triggered only upon complexation. Despite the development of several alkoxyamines-based metal-free radical reactions, the latter are still scarcely used as synthesis tools. Recent results on the reversible activation of alkoxyamines are opening new perspectives of applications in Biology, that is, such molecules can be applied as theranostic agents, and they can be tuned so that either the therapeutic activity[81] or the diagnostic property is favoured.[82,83] Taking into account the generality of the concept and the versatility of alkoxyamines, one may expect many other applications in Biology and (smart) Materials Sciences: orphean diseases, phytochemistry, self-healing materials, switches, etc, as long as specific and selective addressing/activation is performed. External, selective and reversible activation/deactivation of alkoxyamines should open new opportunities for the development of new smart materials or molecular devices.

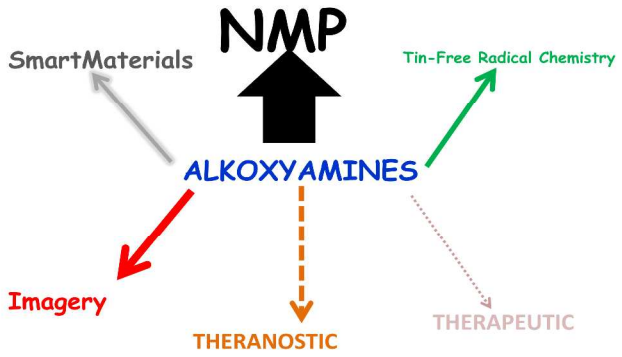


Figure 15. Fields of application for alkoxyamines

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[¥] Since the late 60s, the formation of alkoxyamines via the cross-coupling reaction between alkyl radicals and nitroxides has been well known. See ref. 12 and references therein.

[þ] This term was coined by Daikh et al. See ref. 20.

[§] It has taken researchers two decades to confirm the importance of each stage and each step on the fate of NMP experiments. See ref. 26.

[√] Several preliminary attempts to develop Nitroxide-Mediated Photopolymerization were performed during this decade. See ref. 60-62 as examples.

[∫] Alkoxyamines investigated in refs. 70-73 did not carry protonable sites except the strongly acidic N atom of the C—ON bond which can be protonated only in drastic conditions, as in ref. 68.

[IO] At 200 °C, many other processes of degradation compete with the C—ON bond homolysis.

[Σ] The issue of *Account of Chemical Research* published in September 2011 is devoted to Theranostics.

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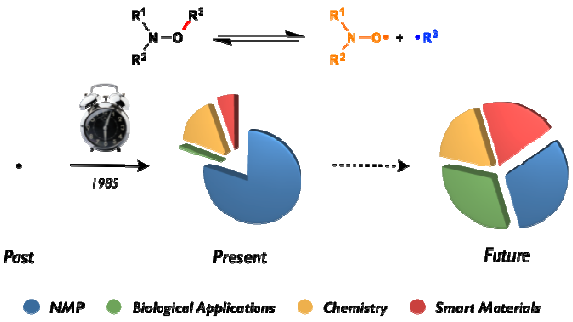
TOC



Sylvain Marque was awarded a Ph.D from Paul Cézanne University (Marseille) in 1996. In 1997, he spent one year as postdoctoral fellow with Prof. D. H. R. Barton at Texas A&M University. From 1998 to 2000, he joined Prof. H. Fischer's team (University of Zürich). In 2000, he was appointed Assistant Professor at University of Provence, and in 2008, he was promoted to a Professorship position. His research is focused on the reactivity of organic radicals investigated by means of EPR, NMR and calculations, and applied in Organic Chemistry, (controlled) Polymerization, Spectroscopy, and Biology.

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