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Design concept for α -hydrogen-substituted nitroxides

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Stable nitroxides (nitroxyl radicals) have many essential and unique applications in chemistry, biology and medicine. However, the factors influencing their stability are still under investigation, and this hinders the design and development of new nitroxides. Nitroxides with tertiary alkyl groups are generally stable but obviously highly encumbered. In contrast, α -hydrogen-substituted nitroxides are generally inherently unstable and rapidly decompose. Herein, a novel, concept for the design of stable cyclic α -hydrogen nitroxides is described, and a proof-of-concept in the form of the facile synthesis and characterization of two diverse series of stable α -hydrogen nitroxides is presented. The stability of these unique α -hydrogen nitroxides is attributed to a combination of steric and stereoelectronic effects by which disproportionation is kinetically precluded. These stabilizing effects are achieved by the use of a nitroxide co-planar substituent in the γ -position of the backbone of the nitroxide. This premise is supported by a computational study, which provides insight into the disproportionation pathways of α -hydrogen nitroxides.

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Persistent nitroxides have intriguing structural and chemical properties^{1–3} and possess a multitude of highly important applications, such as oxidation catalysts^{4–7}, reagents in living polymerization reactions⁸, spin probes in biology⁹, radical traps in mechanistic investigations, spin trapping agents, medicinal agents^{10,11} and in materials chemistry¹². Designing and preparing stable nitroxides, as well as predicting their properties, remains an important challenge that must be met through a combination of computational methods and creativity¹². Most research has been conducted on the archetypical nitroxide TEMPO ((2,2,6,6-tetramethyl piperidin-1-yl)oxyl, Fig. 1) and structurally related compounds. Given these factors, the development of new classes of nitroxides is an enticing and a superbly challenging goal¹³.

TEMPO (3) is a shelf-stable compound and is the catalyst of choice in industry¹⁴ as well as in academia for the oxidation of primary alcohols to aldehydes^{1–7}. It has many applications in evaluating radical formation in biological tissues^{15,16} and is also the trapping agent of choice in mechanistic investigations of chemical processes when a radical intermediate is suspected^{17,18}. Conjugates of TEMPO and other nitroxides are also being evaluated for various medicinal uses^{10,11}. Despite its popularity, it suffers from several shortcomings. For example, it often fails to catalyse the oxidation of secondary or hindered alcohols to carbonyl compounds and is a poor catalyst for polymerization of non-styrenic monomers. This is, at least in part, due to the four methyl groups adjacent to the reactive locus: the nitroxyl moiety. Since most known cyclic nitroxides conserve the four methyl groups flanking the radical function, the preparation of cyclic nitroxides with other substitution patterns would be highly desirable. In addition, chiral nitroxides would be desirable both for catalytic as well as biological applications.

One avenue of investigation for developing more active and tuneable systems would be to reduce the steric hindrance by replacing one or more of the methyl groups with a hydrogen atom. However, α -hydrogen-substituted nitroxyl compounds are notoriously and inherently unstable, and undergo fast

disproportionation in which two radicals react to give one molecule of nitron and one of hydroxylamine (Fig. 2)¹⁹. The magnitude of this challenge was succinctly described in a 2009 review: ‘...nitroxides are prepared by the oxidation of secondary amines that contain no hydrogen atoms on the α -carbons... If the amines carry α -hydrogens, the oxidation products are nitrones, not free-radical nitroxides...’¹.

Given their instability, which imposes severe structural design limitations, it is not surprising that examples of α -hydrogen nitroxides are extremely rare. This is especially evident when compared to the development of, for example, amine and phosphine ligands for transition metal catalysis of which many thousands have been developed²⁰. In fact, we are aware of only two successful designs of α -hydrogen nitroxides that have been reported before this work.

More than 40 years ago, Rassat and Dupeyere²¹ described the first example of bridged bicyclic α -hydrogen nitroxyls, namely 4 and AZADO (5; Fig. 1). These compounds proved to be exceptionally stable. Their stability is believed to be derived from the inability to form a nitron C=N double bond to the bridgehead—an elegant application of Bredt’s rule²². AZADO (5) has recently been shown to be a powerful oxidation catalyst and is now commercially available because of the efforts of Iwabuchi and co-workers^{23–25}, who also reported a number of other nitroxides inspired by the same design concept. Unfortunately, the bridged bicyclic design is not universally applicable. For example, compound 6 reported by Rychnovsky and co-workers²⁶ decomposes rapidly, possibly via C–N bond scission.

The only other reported structural family are a group of acyclic α -hydrogen nitroxides first described in 1996 (refs 27,28) typified here by the polymerization catalysts TIPNO (7) and SG1 (8)^{29,30}. Many examples conforming to this design have been prepared and successfully applied in living polymerization reactions⁸, however, we are unaware of any examples of them being used in oxidation chemistry.

These examples, bicyclic and acyclic, constitute compelling examples of chemical knowledge-based design overcoming the natural tendency of α -hydrogen nitroxides to decompose. It would be desirable to develop a design that would allow the preparation of monocyclic α -hydrogen nitroxides, both from the

Figure 1 | Structures of the α -hydrogen nitroxides. Novel nitroxide families 1 and 2 introduced in this work, TEMPO (3), examples of bridged bicyclic α -hydrogen nitroxides (4), AZADO (5) and (6), and acyclic nitroxides TIPNO (7) and SG1 (8).

Figure 2 | Disproportionation mechanism for α -hydrogen nitroxides.

Proposed disproportionation mechanisms for nitroxides. (Pathway a) direct hydrogen atom abstraction³¹. (Pathway b) SET via the head-to-tail dimer 10 to give ion pair 11/12 followed by proton transfer¹⁹.

basic scientific as well as a practical point of view. One stumbling block to designing new α -hydrogen nitroxides is that there are a few proposed decomposition pathways and there is no consensus as to which one is operative. Ingold and co-workers³¹ first proposed that α -hydrogen nitroxyls decompose by hydrogen abstraction (that is, disproportionation) to give the isolable nitrones **13** and hydroxylamine **14** (Fig. 2, pathway a). An alternative proposal by Braslau and co-workers¹⁹ is that an initial single electron transfer (SET) step takes place to afford an oxoammonium ion **11** and a hydroxylamine anion **12** (Fig. 2, pathway b). The SET may involve the initial formation of a head-to-tail nitroxide dimer **10**. Subsequent proton transfer, from **11** to **12**, would lead to the observed products (Fig. 2)¹⁹. A third possibility³¹ involving a rearrangement of **10** was ruled out by Braslau and co-workers¹⁹ based, *inter alia*, on thermodynamic and stereochemical considerations. It is not clear which of these mechanisms is operative, and the decomposition mechanism may depend on the structure of the nitroxide in question (see detailed discussion below).

It should be noted that, while oxoammonium cations such as **11** are important species inferred in many catalytic oxidative processes, only a few oxoammonium salts, mainly of TEMPO derivatives, have been isolated as discrete stable materials^{1–3}. For fully alkyl-substituted radicals such as **3**, it has been shown that decomposition of the oxoammonium salt occurs predominantly via β -deprotonation by a base^{1,32}. For **3**, the equilibrium between two nitroxides and the oxoammonium ion and hydroxylamine can also be catalysed by acid^{1,32}. Other fully α -substituted nitroxides with highly sterically demanding flanking groups may also undergo C–N bond scission¹⁹.

Herein, a novel design concept based on a combination of stereoelectronic and steric guidelines is presented. A proof-of-concept is provided; it is shown that the design is applicable to two different systems (**1** and **2**, Fig. 1), and two different examples for each class are given. To the best of our knowledge, this paper constitutes the first example of a stable α -hydrogen piperidin-1-yl-oxy and pyrrolidin-1-yl-oxy nitroxides that are not bicyclic. A computational study that underpins the design principles outlined herein, which may be of broad general interest for the understanding of nitroxides, is also reported.

Results

Design concept. A nitroxyl design along the lines of **15** (Fig. 3) was envisioned that would achieve stability by incorporating a stabilizing substituent R^5 on a planar rigid (aromatic) radical backbone. This would lead to an increased activation barrier for disproportionation through a combination of three synergistic effects: (i) The R^5 substituent would push the R^4 substituent out of the backbone/N–O plane. This would place the R^4 substituent in **15** right in the path of approach of a second molecule of **15**, sterically inhibiting hydrogen atom abstraction. (ii) Forcing the R^4 substituent out of the backbone/N–O plane would lead to compression of the H–C–N–O angle. Angle compression below the optimal 90° angle for hydrogen atom abstraction would increase the energy barrier for hydrogen atom abstraction and nitron formation. This is due to poor overlap between the C–H σ -bond being broken and the singly-occupied molecular orbital localized on the N–O bond that will be part of the nitron double bond being formed³³; similar considerations have been put forth to explain the stability of the acyclic radicals of the TIPNO (**7**)/SG1 (**8**) family based on conformational stabilities^{27,34,35}. (iii) During nitron formation the R^4 substituent would move into the plane of the R^5 substituent. This would lead to incipient allylic strain, which would further increase the kinetic barrier to disproportionation irrespective of the mechanism. This

Figure 3 | The design principles used in the design of α -hydrogen nitroxides **1 and **2**.** (a,b) Avoiding the optimal 90° dihedral angle for hydrogen atom abstraction (as in **b** versus **a**). (c) Impediment of the disproportionation of **15** to nitron **16** and hydroxylamine **17** through predominance of a conformer in which the R^4 of two opposing radicals would sterically repulse each other and in which incipient A(1,3) strain would kinetically disfavour nitron formation. These three kinetically stabilizing effects are proposed to be enhanced by placing a sterically hindered R^5 substituent on the backbone of structure **15** that will dispose the R^4 group out of the naphthalene/N–O plane, thus forcing the α -hydrogen atom closer to the plane of the N–O. See text for discussion.

conjecture was inspired by the observation that naphthalenes substituted in the 1 and 8 positions with sterically hindered alkyl groups are deformed out of plane, with concomitant loss of aromaticity, due to allylic strain^{36–39}.

By combining these three diverse and mutually enforcing elements into our design, it was hoped that sufficient kinetic stability of the resulting nitroxides would be achieved to make them stable at ambient temperature. These considerations led to the proposed isoindole structure **1** with a single α -hydrogen and iso-azaphenalene **2** with two α,α' -hydrogen atoms (Fig. 1). It is important to note that simple α -hydrogen nitroxides that do not conform to this design are inherently unstable; for instance, oxidation of piperidine N-oxides with single substituents on C(2) or C(4) results in nitrones^{40–43}.

In order for any nitroxide design to be attractive from a practical point of view, it is essential that the nitroxide be prepared in high yield and in few synthetic steps. Flexible syntheses of both target structures **1** and **2** have been developed. These syntheses potentially afford access to a wide range of compounds of structures with different substituents (Figs 4 and 5). The syntheses described herein are amenable to gram scale assembly of the nitroxide scaffolds and are highly stereoselective.

Preparation of stable α -hydrogen nitroxyl radicals. The challenge of synthesizing isoindole structure **1** bearing a single α -hydrogen atom was addressed first (Fig. 4)⁴⁴. The entire scaffold was assembled in a single synthetic step through the [3 + 2] cycloaddition of commercially available naphthoquinone **18** with imines **19** (R = mesityl (mes) or naphthyl (naph))^{45,46}. It was found that the initial bisnaphthol product **21a,b** is rapidly oxidized to the quinone **22a,b** when exposed to air during workup. Quinones **22a** and **22b** were isolated in 28% and 63%

Figure 4 | Synthesis of isoindole nitroxides 25a and 25b.

Figure 5 | Synthesis of iso-azaphenylene nitroxides 32 and 35. Conditions for preparing **29a**, $R^1 = \text{Mes}$, $R^2 = \text{H}$: mesityl aldehyde (2.5 equiv.), $\text{H}_2\text{N}-R^2 = \text{NH}_4\text{OAc}$ (1.2 equiv.), EtOH, reflux 2 days, 70% yield, >17:1 d.r. Conditions for preparing **29b**, $R^1 = \text{Ph}$, $R^2 = 2,4\text{-dimethoxybenzylamine}$: 1.1 equiv. 2,4-dimethoxybenzylamine (1.5 equiv.), 6 equiv. benzaldehyde, 2 days, and then toluene sulphonic acid (1 equiv.), dichloromethane, 1 day, 95% yield, >17:1 d.r.

yield, respectively, on a gram scale. It was hypothesized that appending TIPS (tri-*iso*-propylsilyl) groups to the hydroquinone oxygen atoms, affording OTIPS group, would provide sufficient bulk for stability. To this end, reduction of the quinones with $\text{Na}_2\text{S}_2\text{O}_4$ followed by treatment of the unpurified hydroquinones with TIPSCl and Hünig's base led to the stable silylated products **23a** and **23b** in 51% and 81% yields, respectively. Oxidation using *meta*-chloroperoxybenzoic acid (*m*CPBA) afforded the hydroxylamines **24a** and **24b** as mixtures with the corresponding nitroxides **25a** and **25b** respectively. The relative configuration of **24a** was determined by X-ray crystallography (see Supplementary Fig. 1). Further oxidation of the hydroxylamine/nitroxide mixtures to the pure radicals using silver oxide or other oxidizing reagents led to decomposition only. However, simply exposing the mixtures to air led to quantitative formation of the desired nitroxides **25a** and **25b**. These radicals were characterized by electron spin resonance (ESR; Supplementary Fig. 2a,b), infrared and high-resolution mass spectrometry (HR-MS). Both radicals are highly stable, remaining unchanged in benzene solution for 2 months without

any reduction in ESR signal amplitudes, nor any sign of decomposition products. The radicals can be isolated as solids by simple evaporation of the solvent and kept as solids for at least 2 months. *This constitutes a proof-of-principle of our design concept.* The ESR spectra have the expected splitting of the N–O system ($a_{\text{N}} = 15.2 \text{ G}$ for **25a** and $a_{\text{N}} = 13.9 \text{ G}$ for **25b**, Supplementary Fig. 2a,b) with additional splitting by the adjacent C–H group ($a_{\text{H}} = 21.8 \text{ G}$ for **25a** and $a_{\text{H}} = 16.3 \text{ G}$ for **25b**), consistent with simulated spectra. In contrast to the marked stability of **25a** and **25b**, oxidation of **22a** with *m*CPBA leads to the formation of a nitroxide that decomposes within minutes (see Supplementary Fig. 17 for the ESR of this radical). Thus, the electronic nature of the naphthyl and the steric requirements of the naphthyl R^4 substituent in **1** (Fig. 1) are important for stability.

In order to test the generality of the design concept, the study was extended to a second design based on the same principles, but imposing an even greater challenge by having two α -hydrogen atoms—one on either side of the nitroxyl function. This led to the *iso*-azaphenylene family **2** (Fig. 1)⁴⁷. This

attractive structural backbone can be efficiently assembled in a single synthetic step (Fig. 5). Betti-type reaction of 2,7-naphthalene diol (**26**) with ammonium acetate or 2,4-dimethoxybenzylamine and variety of aryl aldehydes **28** afforded condensates **29** in excellent yields and with high stereoselectivities ($>17:1$)⁴⁸. The aldehyde may be benzaldehyde or derivatives bearing electron-withdrawing or -donating substituents (see Supplementary Methods). Subsequent triflation of **29a** (R^1 =mesityl) proceeded in 94% yield. Stille coupling of the triflate with tetramethyltin gave **30a** in 95% yield. Phenyl-substituted **29b** (R^1 =phenyl) was converted into the triflate in 95% yield and methylated in 95% yield. Removal of the 2,4-dimethoxybenzyl protecting group using trifluoroacetic acid (TFA) proceeded in 86% yield to give the free amine **30b**.

Oxidation of amines **30ab** to hydroxylamines **31ab** was carried out using *m*CPBA. In both cases, the reaction was complete within minutes, yet the stability of the products was remarkably dissimilar. The less sterically congested hydroxylamine **31b** was isolated in 40% yield and decomposed after purification to give the nitron. In contrast, the mesityl derivative **31a** was isolated in 70% yield after flash chromatography and proved to be completely stable for more than 9 months as a solid. Both hydroxylamines contained minor amounts of the corresponding nitroxide, observed by ESR. The stable mesityl derivative **31a** was characterized by X-ray crystallography (Supplementary Fig. 1) revealing the *trans* relationship of the two R^1 substituents.

Treatment of the hydroxylamine **31b** with silver oxide did not result in the isolation of the corresponding radical. Presumably, the transient radical immediately disproportionated. In stark contrast, oxidation of **31a** led to the formation of stable nitroxide **32**. This radical was isolated in 76% yield after purification by standard flash chromatography with no special precautions and was characterized by HR-MS and ESR. The ESR spectrum (Supplementary Fig. 2c) corroborates the structure with splitting of the N–O system ($a_N=14.5$ G) with additional splitting by the two adjacent C–H groups ($a_{2H}=17.5$ G), consistent with a simulated spectrum. In a benzene solution exposed to air, it has a half-life of 3 days. However, ~2% of the radical still remained in solution (as detected by ESR) after 2 months. In the solid state, the yellow radical is stable for at least 9 months at -15°C exposed to air without any detectable degradation. The compound possesses slight solvatochromism, appearing orange in some solutions, similar to TEMPO (**3**).

A TIPS substituted *iso*-azaphenalene radical **35** was also prepared in this study. Silylation of **29a** proceeded smoothly to afford **33** (Fig. 5). Oxidation with *m*CPBA led to the stable hydroxylamine **34** in 95% yield. Oxidation of **34** with silver oxide gave the free nitroxide **35**. The nitroxide was characterized by ESR (Supplementary Fig. 2d), infrared and HR-MS. X-ray diffraction studies of single crystals of **34** showed that the unit cell contained two different structures differing only by the conformation of the TIPS groups (Supplementary Fig. 1c). Interestingly, this is also reflected in the ESR spectrum of **35** (Supplementary Fig. 2d) that clearly shows two radicals, indicating that interconversion is slow on the ESR timescale. The overlapping spectra were deconvoluted using simulated ESR spectra (Supplementary Fig. 16). Partial coalescence of the ESR spectra could be observed by heating the radical to 80°C in toluene. On cooling to room temperature, the signals again separated, and resolved further by cooling to -20°C (Supplementary Fig. 16). Nitroxide **35** is stable for at least 9 months as a solid.

The applicability and generality of the design concept have thus been demonstrated by the preparation of two different families of nitroxides (**1** and **2**) and two stable examples of each family (**25a**, **25b**, **32** and **35**). We have shown that OTIPS and

methyl groups on the radical backbone stabilize the isoindoline and *iso*-azaphenalene nitroxides. In contrast, the nitroxide derived by oxidation of quinone **22b** decomposes rapidly as do other piperidine hydroxylamines upon oxidation^{40–43}. The design principles outlined in the introduction were then evaluated, taking advantage of the power of computational studies of the nitroxides already demonstrated to be stable^{12,49,50}.

Computational study into the stability of the nitroxides. The principal decomposition pathway of α -hydrogen nitroxides is disproportionation to give one molecule of nitron **13** and one of hydroxylamine **14** as shown in Fig. 2. Three different mechanisms of disproportionation have been proposed, namely: (i) direct hydrogen atom abstraction by one radical from the other to give the products in a single step (Fig. 2, pathway a)³¹, (ii) head-to-tail dimer formation (**10**), SET to give one molecule of oxoammonium cation **11** and one of hydroxylamine anion **12** and subsequent proton transfer to give the products (Fig. 2, pathway b)¹⁹ and (iii) formation of a head-to-head (O–O) dimer **10** followed by a concerted rearrangement in a second step to give **13** and **14** (ref. 31). The third mechanism has been rejected based on thermodynamical and stereochemical arguments¹⁹. However, the other two mechanisms are still under consideration. Indeed, it is possible that different nitroxides may decompose by different mechanisms depending, *inter alia*, on substituent effects, much like the mechanism of nucleophilic substitution changes from S_N2 to S_N1 on going from methyl iodide to *tert*-butyl iodide.

All density functional theory (DFT) calculations were performed at the SMD(acetonitrile)-RIJCOSX-DSD-PBEB95/def2-TZVP//DF-PBE_{D3BJ}/def2-SVP level of theory (Supplementary Methods, Computational Methods section). On performing the calculations, certain assumptions were made in order to evaluate computationally pliable systems at as high a level of theory as practically possible. The TIPS groups, while hydrolytically stable, result in a large number of degrees of freedom, as noted in the X-ray crystallography of **34** and ESR spectrum of **35** (*vide supra*), making calculations very demanding. Consequently, it was assumed that calculations on models in which the TIPS groups in radicals **25a** and **35** are replaced by the simpler trimethylsilyl (TMS) groups, as in **36** and **37** (Fig. 6), would only have a minor impact on calculated energies and properties but would significantly reduce computational time. The validity of this assumption can be seen in that the overall driving force for the disproportionation of **35** and **37** are within 1 kcal mol^{-1} of each other (Table 1, column 2). For comparison, the disproportionation of the hypothetical *iso*-azaphenalene **38** (Fig. 6) of family **2** was also studied. Compound **38** should be unstable based on the experimental observation that the phenyl-substituted **31b** spontaneously decomposes. Compound **38** would have a much smaller tendency for incipient allylic strain when transitioning into the corresponding nitron **13/16** (Fig. 3), less steric hindrance and higher conformational flexibility, thus being able to achieve the orbital overlap required for hydrogen abstraction (Fig. 2, pathway a and Fig. 3a). In contrast, it was not expected to have a dramatically different ability to undergo SET (Fig. 2, pathway b) compared with the other radicals studied.

Importantly, in all cases, the disproportionation is energetically favourable (Table 1, column 2). This shows clearly that the stability of the nitroxides is due to kinetic factors. In contrast, the SET from the radicals to give the oxoammonium **11** and hydroxylamine anion **12** (Fig. 2, pathway b) are all strongly endergonic (Table 1, column 3). Therefore, it is reasonable to rule out the SET pathway, leaving the hydrogen-atom-transfer mechanism (Fig. 2, pathway a) as the most likely mechanism. Further support may be obtained from the plots of the Mulliken

Figure 6 | DFT optimized structures of the nitroxides 32 and 35–38. Hydrogen atoms, other than the α -hydrogens, have been omitted for clarity. (Colour code: C—grey, H—white, N—blue, O—red, Si—light blue).

Table 1 | Calculated energies for radicals 32, 35–38*.

Radical	Disproportionation	SET to give 11/12	Radical pair precomplex	$\Delta G_{298}^{\ddagger}$
36	−20.8	76.6	27.2	38.4
32	−25.4	72.3	13.0	44.5
38	−12.5	69.6	−17.2 [†]	6.6
35	−24.3	73.3	— [‡]	— [‡]
37	−25.0	71.4	— [‡]	— [‡]

SET, single electron transfer.

*Reaction free energies ($\Delta G_{298,\text{sol}}^{\ddagger}$, kcal mol^{−1}) for the disproportionation of two nitroxides to one nitron and one hydroxylamine, SET to give **11** and **12**, formation of the radical pair precomplex and the height of the transition state barrier for hydrogen atom abstraction via pathway a ($\Delta G_{298}^{\ddagger}$).

[†]Attempts at optimization of the radical dimer led directly to the nitron/hydroxylamine hydrogen-bonded dimer instead.

[‡]Not calculated.

charges (Supplementary Figs 3–5) on the fragments during the hydrogen-transfer processes (*vide infra*). The charge on the hydrogen atom being transferred remains fairly constant at $\sim 0.2e^-$, while there is not any significant charge accumulation on either fragment.

The direct hydrogen abstraction mechanism (Fig. 2, pathway a) is associated with a large reaction barrier for the stable radicals (Table 1, column 5). The structures of the **32** and **36** radical pair precomplexes, where the oxygen atom of one radical is pointing towards the α -hydrogen of the second, were first optimized (see Table 1, column 4 for energies of formation). The hydrogen-transfer transition states could not be found for these nitroxides, likely because of the flatness of the potential energy surface at the level of theory used for geometry optimizations and because of the strong exergonicity of the disproportionation reaction. Therefore, relaxed scans along the hydrogen abstraction reaction coordinate were performed, fitting the points around the maximum to a third-order polynomial, giving barriers, approximating the transition states, of $\Delta G_{298}^{\ddagger} \approx 44.5$ and 38.4 kcal mol^{−1}, respectively (Fig. 7 and Table 1, Column 5); these values account for the endergonic formation of the initial

radical dimers (Table 1, column 4). Note that the value of 38.4 kcal mol^{−1} is for the truncated radical **36** where the TIPS of **25a** (Fig. 4) is replaced by the smaller TMS (Fig. 6). One would expect that inclusion of TIPS instead of TMS would substantially increase the barrier. In contrast, the related relaxed scan for hypothetical radical **38** revealed a barrier of only $\Delta G_{298}^{\ddagger} \approx 6.6$ kcal mol^{−1}, indicating that this reaction should proceed very rapidly; in fact, optimization of the radical pair precomplex did not lead to the analogous radical pair but rather hydrogen-bonded nitron and hydroxylamine products.

In order to verify the electronic state of the radical dimer pair, NEVPT2-CASSCF(8,8) calculations were performed for the radical pair precomplex of **38** for the structure from the relaxed scan where the C–H bond is closest to a typical C–H bond. It is reasonable to assume that the other radicals will have similar behaviour. Unfortunately, the other nitroxides are far too large to be amenable to a CASSCF treatment. These calculations show that the electronic ground state has a closed-shell singlet and the dominant configuration has all electrons paired with a weight of 84% and only small contributions from other configurations. The triplet state is 3.538 eV (3.293 eV for CASSCF) higher in energy. Thus, it is reasonable to treat the radical dimers as closed-shell singlets. If one examines the electronic structure of the precomplex, one notes that there is a hydrogen bond between the oxygen of one nitroxide and the hydrogen being abstracted on the other; the Mayer bond index between these two atoms is 0.33 . In forming the hydrogen bond, $0.58 e^-$ of charge (Mulliken partial atomic charges) is transferred from one nitroxide to the other. Nevertheless, this would be consistent with the formation of the hydrogen bond as an integral first step in hydrogen abstraction rather than SET.

A major contribution to the large barriers is unfavourable steric interactions between the two radicals in the radical pairs. Supplementary Table 1 lists the steric interaction energies (ΔE_{steric}) of the various radical dimers. While **38** shows a very small ΔE_{steric} , the radical pair of **32** and the disproportionation TS are relatively high in energy. This will have a significant impact on the reaction, making the disproportionation of **32**

Figure 7 | Comparison of dihedral angle changes during disproportionation. Relaxed scans of the reaction energy for the hydrogen atom abstraction for (a) **36**, (b) **38**, (c) **32** as a function of the O–H (**36** and **32**) or C–H (**38**) distance (right axis, red). Also shown are plots of the ϕ (H–C–N–O) dihedral angle (left axis, blue) during the reaction.

unfavourable. The same tendency is observed for **36**. This is also apparent from the NCI plots (Supplementary Fig. 7). In the NCI plot for **32**, there are significantly more weak interactions between the two fragments than in the NCI plot for **38**. In addition, from the structures presented, one notes that the radical pair of **32** involves two distinct radicals, whereas the equivalent structure for **38** is an O–H $\cdots$ O hydrogen-bonded hydroxylamine–nitron pair—the disproportionation products (Fig. 2). The equivalent radical pair could not be located for **38**, likely because of the low barrier and high exergonicity for disproportionation. In the disproportionation transition state for stable radical **32** (Supplementary Fig. 8), the structure is clearly an early transition state with the C–H bond maintained and with a strongly attractive (blue) O $\cdots$ H interaction.

Figure 7 shows changes in the angles between the C–H bond being broken in the disproportionation step and the N–O bond (that is, the ϕ (H–C–N–O) dihedral angle). As noted above, the ideal situation for hydrogen atom abstraction would be when

there is maximal overlap between the C–H bond and the N–O singly-occupied molecular orbital (Fig. 2), since one of the electrons from the C–H bond forms part of the C=N double bond in the nitron product, the other electron coming from the N–O radical. Thus, this process would be facilitated by a $\pm 90^\circ$ dihedral angle between these two bonds. This angle (ϕ) is plotted against the reaction coordinate for each radical in Fig. 7. For the radical monomer of **32**, the ϕ angles are -51° and -69° . As the dimer is formed, the N–O is pushed out of the plane of the naphthalene ring, reaching -110° when the hydrogen is abstracted (Fig. 7c). Similar tendencies are observed for the other radicals. For **38** (Fig. 7b), the ϕ angles are -42° and -53° . As the dimer is formed, it moves towards -90° as the hydrogen atom is abstracted. This conformationally flexible compound has the lowest barrier of the studied systems. For all the radical dimers, ϕ is 15 – 20° from the ideal energy conformer for hydrogen abstraction when the abstraction takes place (Compare Fig. 7 with Figs 2b and 5). For *iso*-azaphenanthrene **32**, it appears that it is not possible for the C–H bond to move into periplanarity with the N–O orbital and thus when abstraction takes place the barrier is higher than it would be in the ideal case as found in **38** (Fig. 7c). For radical **36**, the situation is less clear as ϕ continues to approach 90° during the hydrogen abstraction (Fig. 7a). This particular effect is likely less important for the stability of this specific radical.

In combination, these results indicate that hydrogen atom abstraction is the active disproportionation mechanism for systems **1** and **2**. Ingold and co-workers^{31,51} in a classical study showed that the decomposition of diethylnitroxide takes place via second-order or pseudo-second-order dependence on the radical concentration, that diamagnetic dimers (presumably of type **10**) are formed, and that the rate of radical decay is inversely proportional to solvent polarity (being roughly 30 times faster in *iso*-pentane than water). This solvent effect would appear to be inconsistent with a mechanism involving the formation of ion pair **11/12** (Fig. 2, pathway b) and could be in line with a hydrogen atom abstraction mechanism (Fig. 2, pathway a). It has been proposed that head-to-tail dimers occur on the path to product formation, specifically as a step preceding ion pair formation. Nonetheless, neither the observation of radical dimers in solution nor the low pre-exponential factors found in Ingold's Arrhenius analysis imply that dimer **10** is an intermediate on the direct reaction pathway to the nitron and hydroxylamine (Fig. 2, pathway b) rather than simply a competing equilibrium. Our calculations did not proceed through dimers such as **10**, rather at the highest point along the reaction coordinates (Fig. 7 and Table 1), radical $\cdots$ radical dimers were observed. Obviously, more work is required to make any definite conclusions, however, based on the present calculations and the earlier observations by Ingold, it is reasonable that the hydrogen atom abstraction mechanism may be the predominant disproportionation pathway in other systems as well.

Nitroxide properties and applications. In order to evaluate the potential of the new radicals in applications such as catalysis, the bond dissociation energies (BDE) and redox potentials⁵² of the radicals were calculated. The calculated redox potentials of **32**, **35**–**38** obtained are similar to that calculated for TEMPO (Table 2). The ability of the radicals to serve as a catalyst in oxidation reaction might therefore be envisioned.

Indeed, nitroxides **25a**, **25b**, **32** and **35** are able to reversibly cycle between their reduced (hydroxylamine) and nitroxide states, as shown by their use as a co-catalyst in the aerobic copper-catalysed oxidation of benzyl alcohol using the conditions developed by Hoover and Stahl⁵³. These conditions have been shown to involve the nitroxides alternating between these two

Table 2 | Calculated homo- and heterolytic BDE (kcal mol⁻¹) of the radicals in the gas phase and in acetonitrile, and the redox potentials (eV) in acetonitrile.

Radical	3	36	32	35	37	38
<i>Solution BDE</i>						
Heterolytic	57.8	57.9	56.4	59.6	63.9	48.2
Homolytic	57.6	55.3	59.0	60.5	58.5	51.8
<i>Gas phase BDE</i>						
Heterolytic	365.1	350.8	355.4	355.9	359.9	355.3
Homolytic	57.7	52.3	60.1	61.6	59.4	50.7
<i>Redox potential</i>						
Oxidation	-0.35	-0.89	-0.60	-0.45	-0.66	-0.61
Reduction	-2.18	-2.29	-2.06	-2.14	-2.41	-2.02

Table 3 | Catalytic aerobic oxidation of benzyl alcohol.

Nitroxide	Reaction time (h)	T (°C)	Yield (%)
3	3	25	95
25a	6	55	82
25b	1.5	25	92
32	2	25	96
35	1	25	96

BiPy, Bipyridine; NMI, N-methylimidazole.

oxidation states, and between a copper bound and a free state⁵⁴. Oxidation of benzyl alcohol using nitroxides **25b**, **32** and **35** is complete within 1–2 h at room temperature. For comparison, oxidation using TEMPO, performed in parallel, requires 3 h for complete conversion under the same conditions.

In contrast, nitroxide radical **25a** requires heating to 55 °C and 6 h reaction time. This is because of the precipitation of a nitroxide–copper complex at room temperature. Partial dissolution of the precipitate could be observed along with a colour change from green (copper(II)) back to red–brown (copper(I)) at 55 °C. Thus, the reaction time and the temperature required for **25b** results from solubility limitations and not reactivity. Less than 10% conversion takes place with CuBr/bipyridine/NMI at 55 °C for 6 h in the absence of a nitroxide.

This study demonstrates the ability of all four radicals to cycle between hydroxylamine and radical oxidation states at least 20 times (that is, with a TON of at least 20). The preliminary results presented here are useful for establishing the potential feasibility and future work on this catalytic system. The nitroxides in this study were studied with stability in mind rather than catalytic activity; however, the data shown in Table 3 indicates that high catalytic efficiencies are possible. Since the syntheses of radicals **1** and **2** (Figs 4 and 5) are highly modular, this allows for the easy preparation of a diverse family of nitroxides in terms of the R¹–R⁵ substituents (Fig. 1). It should therefore be possible to design nitroxides of type **1** and **2** with high catalytic efficiencies. Research in this direction is already underway.

Conclusions

A new concept for the design of α -hydrogen-substituted nitroxides of two distinct structural families—**1** and **2**—has been developed (Fig. 1). This design is based on the ability of a substituent in the γ position of the radical (R⁴ in **1** and R⁶ in **2**) to interact with the α substituent, thereby inhibiting disproportionation through a combination of steric and stereoelectronic effects. The compounds prepared are stable for months in the solid form.

The principles outlined and verified experimentally are supported by a thorough computational study. To the best of our knowledge, this study is the first to investigate *in silico* the two prevalent mechanisms for nitroxide disproportionation. The hydrogen atom abstraction mechanism proposed by Ingold and co-workers³¹ was identified as being the most likely mechanism for the decomposition of nitroxides of types **1** and **2**. These results may have significance for other α -hydrogen nitroxides. The nitroxides of types **1** and **2** are shown to possess BDE and redox potentials as expected for nitroxides, which indicates that they should be useful in many applications for which nitroxides are suitable. Catalytic proficiency of these compounds is demonstrated in a preliminary study.

This report constitutes a design concept for cyclic α -hydrogen nitroxides, that is, nitroxides that are not bicyclic like AZADO (**5**) or acyclic like TIPNO (**7**). The design principles outlined in this paper are likely not restricted to nitroxides **1** and **2**, and may be applied to the preparation of other nitroxides. The novel nitroxides of types **1** and **2** can be prepared in a highly efficient manner and in high yields. The flexibility of the synthesis allows for simple modification of the parent structures for tailored applications. In the present paper, the catalytic activity of the novel nitroxides was demonstrated, proving their ability to cycle between radical and hydroxylamine oxidation states. Since these compounds are chiral, it is especially attractive to consider potential applications in asymmetric catalysis^{25,26,55} and as probes for biological studies. Indeed, multiple applications in catalysis, biology and medicine may be foreseen; however, this is beyond the scope of the present communication and will form the basis of further reports.

Methods

For general, synthetic and computational methods and characterization data see Supplementary Methods section.

For NMR spectra of the compounds in this article, see Supplementary Figs 18–67.

For ESR spectra of the compounds in this article, see Supplementary Figs 2 and 9–17.

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Author contributions

M.A. and S.B. designed and carried out the experiments. M.A.I. did the DFT calculations and helped to write the manuscript. H.T. participated in designing and carrying out the experiments. B.T. performed the ESR measurements. L.J.W.S., M.B. and N.F. performed the X-ray crystallography. A.M.S. invented the concepts presented here, designed the experiments, supervised the work and wrote the manuscript.

Additional information

Accession codes. Accession codes: The X-ray crystallographic coordinates for structures **24a**, **32** and **34** reported in this Article have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition number CCDC 1037250, 975284 and 975285. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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