CONSPECTUS: Selective syntheses are now available for compounds of many classes, based on C-centered radicals, exploiting a diverse range of mechanisms. The prospect for chemistry based around N- and O-centered radicals is probably more favorable because of the importance of heterocycles as biologically active materials. Heteroradical chemistry is still comparatively underdeveloped due to the need for safe and easy ways of generating them. Oxime esters appeared promising candidates to meet this need because literature reports and our EPR spectroscopic examinations showed they readily dissociated on photolysis with production of a pair of N- and O-centered radicals. It soon became apparent that a whole suite of benign oxime-containing molecules could be pressed into service. The bimodality of the oxime motif meant that by suitable choice of functionality the reactions could be directed to yield selectively products from either the N-centered radicals or from the O-centered radicals.

We found that on one hand photolyses of acetophenone oxime esters of carboxylic acids yielded alicyclics. On the other hand, aromatic and heteroaromatic acyl oximes (as well as dioxime oxalates) afforded good yields of phenanthridines and related heterocycles. Easily prepared oxime oxalate amides released carbamoyl radicals, and pleasingly, β-lactams were thereby obtained. Oxime carbonates and oxime carbamates, available via our novel 1,1’-carbonyldiimidazole (CDI)-based preparations, were accessible alternatives for iminyl radicals and hence for phenanthridine preparations. In their second modes, these compounds proved their value as precursors for exotic alkoxycarbonyloxyl and carbamoyloxyl radicals. Microwave-assistance was shown to be a particularly convenient procedure with O-phenyl oxime ethers. The iminyl radicals generated from such precursors with alkene, alkyne, and aromatic acceptor substituents furnished pyrrole, quinoline, phenanthidine, benzonaphthiridine, indolopyridine, and other systems. Microwave irradiations with 2-(aminoaryl)alkanone O-phenyl oximes enabled either dihydroquinazolines or quinazolines to be obtained in very good yields.

The fine quality of the EPR spectra, acquired during photolyses of all the O-carbonyl oxime types, marked this as an important complement to existing ways of obtaining such spectra in solution. Quantiations enabled SARs to be obtained for key reaction types of N- and O-centered radicals, thus putting mechanistic chemistry in this area on a much firmer footing. Surprises included the inverse gem-dimethyl effect in 5-exo-cyclizations of iminyls and the interplay of spiro- with ortho-cyclization onto aromatics. Insights into unusual 4-exo-cyclizations of carbamoyl radicals showed the process to be more viable than pent-4-enyl 4-exo-ring closure. Another surprise was the magnitude of the difference in CO₂ loss rate from alkoxycarbonyloxyl radicals as compared with acyloxy radicals. Their rapid 5-exo-cyclization was charted, as was their preferred spiro-cyclization onto aromatics. The first evidence that N-monosubstituted carbamoyloxyls had finite lifetimes was also forthcoming.

It is evident that oxime derivatives have excellent credentials as reagents for radical generation and that there is ample room to extend their applications to additional radical types and for further heterocycle syntheses. There is also clear scope for the development of preparative procedures based around the alkoxyl and aminyl radicals that emerge downstream from oxime carbonate and oxime carbamate dissociations.
for meagerly studied N- and O-centered species thereby giving entry to diverse heterocycle systems.

Sporadic reports have appeared since the 1970s of UV photolyses of oxime esters of aliphatic carboxylic acids yielding iminyl and carbon-centered radicals. The group of Hasebe had developed arylations and chlorinations from benzophenone oxime esters. Zard had generated iminyl radicals from cyclobutanone and other oxime esters in several ingenious ways. We recognized that a whole suite of oxime-containing molecules could be employed, extending the field well beyond oxime carboxylate esters. Specific oxime-containing structures were discovered that deliver a sizable corpus of useful and esoteric radicals spanning C-, N- and O-centered types. Our investigation covered two classes: first, oxime carbonyls, containing the \( \text{C} = \text{N} - \text{OCH(O)} \) unit, and second, oxime ethers, containing the \( \text{C} = \text{N} - \text{OAr} \) unit. Scheme 1 shows five distinct types of oxime carbonyls (1–5) that we have investigated with their main synthetic routes.

The outstanding property of oxime derivatives is their bimodality, which enables them to cleave to two species centered on different atoms. Varieties designed with small Z (Me, OEt, OPh) are effective sources of preparatively useful iminyl radicals because the byproducts are small, volatile, or otherwise easily removed (MeH, HOEt, HOPh). In the second mode, R1 and Ar are chosen such that the resulting byproducts \( [\text{R}1\text{ArC} = \text{NH}, \text{R}2\text{ArC} = \text{O}] \) are small or volatile and easily separated, thus facilitating preparations mediated by O-centered radicals.

The X-ray crystal structures for particular examples of oxime carbonyls revealed that in each case extended all-trans structures were adopted with the \( \text{ArC} = \text{N} - \text{OCH(O)} \) unit close to planar (Figure 1). This assisted \( \pi - \pi \) stacking between the aromatic rings of the oxime and the 4-methoxyacetophenone (MAP) used as photosensitizer and thereby promoted energy transfer. The \( \text{N} - \text{O} \) bond lengths were somewhat longer than in oximes themselves, and this was certainly consistent with their ready scission.

Theoretical calculations (CASPT2/6-31G**//CASSCF/6-31G** level) on model acyl oximes pointed to photoexcitation populating a singlet state. Relaxation then led directly to \( \text{N} - \text{O} \) bond breaking, due to the coupling between the imine \( \pi^* \) and the \( \text{N} - \text{O} \) \( \sigma^* \) orbitals.

The second main class that we investigated was oxime ethers, and Scheme 2 shows types 6–8 containing alkenyl, aromatic, and iminyl substituents. Concurrently with our study, Narasaka and co-workers showed that ring closure of \( \gamma,\delta \)-unsaturated or \( \beta \)-aryl oximes was induced by a single electron transfer with Cu or phenolic reagents to give various pyrroles, quinolines, and carbolines. Dihydropyrroles were also prepared by photolytic reactions of similar oxime ester types. Remarkable parallels and counterparts to this radical chemistry can also be found in palladium and copper catalyzed reactions of specific oxime esters.
2. THE BIMODALITY OF OXIME ESTERS AND DIOXIME
OXALATES: ALICYCLIC AND HETEROCYCLIC
PREPARATIONS

For preparative purposes, thermal reactions would be convenient and desirable, but in practice all oxime carbonyls resisted thermal methods, and clean radical generation was not achievable either by conventional heating or by MW irradiation or even on flash vacuum pyrolysis. On the other hand, UV photolyses led to selective N−O scission with generation of iminyls and acyloxyl radicals. The iminyls primarily ended up as imines (or their ketone hydrolysis products) after H atom abstraction from solvent (Scheme 3).

The acyloxyls lost CO2 extremely rapidly releasing C-centered radicals, for further transformations. An aromatic ring adjacent to the imine in 1 and 3 was found to be necessary for efficient UV harvesting. Furthermore, electron-releasing 2- or 4-MeO-substituents further improved efficiency, as did the inclusion of MAP photosensitizer. Pri-Alkyl, sec-alkyl, and tert-alkyl radicals, as well as resonance-stabilized allyl or benzyl radicals and even σ-radicals such as CF3 and cyclopropyl, were readily generated. Radicals having hex-5-enyl type acceptors underwent rapid 5-endo ring closures affording alicyclics in useful yields on H-abstraction from solvent (Scheme 3). Overall the process amounted to a clean decarboxylative route from carboxylic acids to alicyclics.

Alonso et al. tapped into the alternative iminyl generating mode with acyl oximes and described syntheses of phenanthridines, including natural products trisphaeridine and vasconine, as well as heterocyclic systems (Scheme 4). The CO2 and methane, derived from the accompanying MeCO2• radicals, volatilized away.

3. OXIME OXALATE AMIDES: ENTRY TO β- AND
γ-LACTAM MANIFOLDS

Photolyses of toluene solutions of individual oxime oxalate amides 2a (Scheme 1) with MAP delivered, after rapid CO2 loss, carbamoyl (aminoacyl) radicals 21a–c. The N-butenyl example was also easily made from the corresponding ketones, hydrolyzed or degraded comparatively readily but nevertheless functioned as atom-efficient sources of iminyl radicals because the only byproduct was CO2. Photolyses of dioxime oxalates containing butenyl acceptors released iminyl radicals that underwent 5-endo cyclizations to afford 3,4-dihydropyrroles in good yields (Scheme 5). Ar groups adjacent to the imine unit were again necessary, but access to dihydropyrroles without 2-aryl substituents was also gained by means of unsymmetrical dioxime oxalates in which just one lobe contained an acetophenone (or benzaldehyde) oxime to harvest light. Phenanthridines were obtained via the dioxime oxalates derived from biphenyl ketones (Scheme 5).
21a readily cyclized producing 2-oxopyrrolidinylmethyl radical 22a and hence 1-benzyl-3-methylpyrrolidin-2-one 23a in high yield.17 Radical cyclizations in the 4-exo mode producing strained four-membered rings are not usually viable because the reverse ring-opening dominates.18 The equilibrium can be biased in favor of the ring-closed product by rapid trapping of the cyclized radical or by other means.19 The four-membered azetidinone ring system occurs in several families of powerful β-lactam antibiotics. Remarkably, no less than four radical-based disconnections for this system have been investigated.19 We found that the allyl-type carbamoyl radicals 21b and 21c cyclized readily enabling good yields of the corresponding azetidin-2-ones 23b and 23c to be obtained as mixtures of stereoisomers (Scheme 6).

The hydroxyl substituents in 23b,c were a welcome infusion of useful functionality that was likely due to electron transfer from the ring-closed radicals 22b,c to MAP, with the production of the corresponding carbocations, which then reacted with moisture. That radical 21d was produced upon UV irradiation of 2-alkenyl functionalized thiazolidine oxalate amide 2d (Scheme 7) was confirmed by EPR spectroscopy, but cyclization failed and none of 3-isopropyl-penicillin 22d could be isolated. Cyclizations onto oxime ether acceptors were known to be faster than onto alkenes, but again, although carbamoyl radical 21e was spectroscopically observed on UV irradiation of 2e, none of the penicillin derivative 22e could be obtained.20 Evidently 4-exo-cyclization is rendered more difficult by the adjacent five-membered thiazolidine ring. On UV irradiation of noncyclic precursor 2f, both carbamoyl intermediate 21f and its ring-closed azetidinylmethyl radical counterpart 22f were duly observed, showing the viability of this route to β-lactams (Scheme 7).20,21

4. THE DUAL ROLE OF OXIME CARBONATES AS IMINYL AND O-CENTERED RADICAL PRECURSORS

The bimodal character of oxime carbonates 4 enabled them to be deployed either for the production of iminyl radical derived products or for O-centered radical processes.22,23 In the first mode, phenanthridine derivatives 26a,b were isolated from UV photolyses with biphenyl-2-carbaldehyde O-ethoxycarbonyl or O-phenoxycarbonyl oximes 24a,b (Scheme 8), although significant amounts of biphenyl-2-carbonitrile 25 accompanied the phenanthridines.

Scheme 7. Towards Penicillin and β-Lactam Antibiotics

The nitrile 25 was probably produced by a competing pericyclic mechanism (Scheme 8), and in order to disrupt the intramolecular H-bonding in 24, t-butanol was employed as solvent. Pleasingly, this resulted in a greater yield of phenanthridine 26, but some nitrile 3 still interfered. To avert this, a methyl group was introduced as in 27, thus blocking the electrocyclic pathway. Good to excellent yields of phenanthridines 28, 4-methylfururo- and thieno-quinolines 29a,b, and 5-
methylbenzofuro- and thieno-isoquinolines \(30a,b\) were derived from 27 and analogous oxime carbonates (Scheme 8).

Benzaldehyde and acetophenone oxime carbonates were deployed in mode 2 as sources of the rarely studied O-centered alkoxycarbonyloxyl radicals \(\text{OC(O)OR}^*\). Previous EPR and LFP observations with fragile dialkyl peroxycarboxylates \(24,25\) and \(N\)-hydroxy-\(2\)-thiophene-2-thione carbonate precursors \(26\) had shown that they added rapidly to alkenes and aromatics and that decarboxylation was relatively slow. We found that UV photolyses of \(O\)-allyl type oxime carbonates 31 and 36 delivered 1,5-dioxolan-2-ones 33 and 37 in low yields accompanied by allyl alcohols 35 and 38. Precursors 39–41 were designed to yield pent-4-enoxy type radicals, after \(CO_2\) loss from the initial alkoxycarbonyloxyls. Pent-4-enoxy radicals were known to undergo 5-exo-cyclizations very rapidly, \(37\) and hence, had they been produced, tetrahydrofuranyl derivatives should have been formed. In each case, however, only alcohols \(42–44\) were obtained (Scheme 9), so we concluded that the alkoxycarboxyl radicals rapidly abstracted H atoms producing unstable alkyl carboxylic acids such as 34, which speedily decomposed with formation of \(CO_2\) and alcohols.

**5. OXIME CARbamATES RELEASE A TRIAD OF IMINYL, CARBAMOLOXYL, AND AMINYL RADICALS**

Oxime carbamates \(5\) (Scheme 1) prepared from secondary amines by our novel phosgene free method were stable and readily handled, but those from primary amines were difficult to purify and degraded comparatively quickly. Photodissociations of their \(N-O\) bonds released iminyl radicals and fragile carbamoyloxyl radicals \(48,28\). Phenanthridines \(46\) were prepared via iminyl radicals generated from diethylcarbamoyloximes \(45\) in much the same way as with oxime esters (Scheme 10).

**Scheme 10. Reactions of Iminyl and Aminyl Radicals Derived from Oxime Carbamates**

Only aminyls \((R_1R_2N^*\) had been detected in previous approaches to carbamoyloxyl radicals. \(25,29\) Our spectroscopic investigations with oxime carbamates indicated that, above room temperature, both \(N\)-alkyl and \(N,N\)-diarylcarbamoyloxyls cleanly lost \(CO_2\) and produced aminyl radicals such as \(49\) (Scheme 10).

**6. MICROWAVE MANIPULATIONS WITH O-PHENYL OXIME ETHERS**

Oxime ethers, in contrast to oxime esters, did not dissociate on UV irradiation. \(30\) On heating at 150 °C, however, \(O\)-benzyl ketoximes \((R_1R_2C=N-O-C_6H_5)\) furnished products from both \(O\)-C and \(N\)-O bond scission. \(31\) Promisingly, aryl and alkyl \(O\)-phenyl oxime ethers \((R_1R_2C=N=OPh)\) underwent clean \(N-O\) bond homolyses at moderate temperatures yielding iminyl and phenoxyl radicals. \(32\) The resonance stabilization of the released phenoxyl radical ensured this selective bond scission.

\[ R_1R_2C=N=OPh \rightarrow R_1R_2C=N^* + PhO^* \]

Synthetic methodology with conventional heating was unsuccessful because of the long reaction times and complications from side processes. Microwave (MW) methods often promote more efficient reactions, \(32\) and a good number of MW assisted organic syntheses (MAOS) involving radicals have been described. \(33\) Thermolyses of \(O\)-phenyl oxime ethers were dramatically improved by MAOS techniques leading to superior preparations of several types of heterocycles. MW irradiation at 160 °C of precursors \(6\) in toluene solution containing 1-ethyl-3-methylimidazolium hexafluorophosphate (emimPF\(_6\)) as ionic liquid (IL), promoted efficient dissociations to iminyl and phenoxyl radicals. The phenoxyl radicals abstracted H atoms from the toluene solvent, and the resulting phenol was easily separated.

This MAOS tactic with alkenone \(O\)-phenyl oxime ethers \(51\) produced dihydropyroles \(52\) in very good yields, \(34\) and alkynyl acceptor \(53\) furnished pyrrole \(54\) (Scheme 11). Iminyl radical ring closures onto aromatic acceptors, for example, \(55\), were also easily accomplished under MAOS conditions leading to quinoline derivatives, phenanthridines \(56\), benzonaphththridines \(57\), benzothienoquinoline \(58\), indolopyridine derivative \(59\), and tetrahydroindoloquinoline \(60\) (Scheme 11).

Diaza-heterocycles were made by an extension of this strategy employing imine-functionalized \(O\)-phenyl oxime ethers. \(35\) The...
architecture of iminyl-oxime ethers 62 was potentially suitable for iminyl ring closure to either indazole or quinazoline structures. MW irradiation was known to assist the formation of imines; therefore the step yielding imines 62 was integrated with MW generation of iminyl radicals 63 so as to combine the whole sequence in one pot (Scheme 12). This protocol with oxime ethers 61 and aldehydes delivered dihydroquinazolines 65 in good to excellent yields (Scheme 12). Iminyl radicals 63 ring closed onto the C=N bond with exclusive production of quinazolin-1-yl radicals 64; indazoles were never detected. This is likely because aminyl radicals 64 are more resonance stabilized and because of a polarity mismatch in the S-exo approach of the nucleophilic iminyl radical to the nitrogen atom of the imine. Reactions with aliphatic aldehydes were very efficient; somewhat lower dihydroquinazoline yields were obtained with aromatic and heterocyclic aldehydes, but most ketones failed to react.

There were indications that imine formation was incomplete, so since ZnCl_2 was known to promote this, submolar equivalents were included, and forthwith excellent product yields were obtained with aliphatic, aromatic, and heterocyclic aldehydes. The surprising outcome, however, was that quinazolines 66 were formed directly, rather than dihydroquinazolines (Scheme 12). This was attributed to a lowering of the pK\textsubscript{a} of the proton at the C-position by coordination of Zn(II) to the iminyl N-atom of radical 64, hence facilitating deprotonation and aromatization to 66.

This protocol also worked well for oxime ethers with a variety of substituents in their anilinic units. With ketone reaction partners, the dihydroquinazoline products were usually contaminated with byproducts, and yields were poor.

7. INTERROGATION OF RADICAL MOTIONS AND MECHANISMS BY EPR SPECTROSCOPY

All members of the carbonyl oxime suite on UV irradiation in solution with MAP, in the resonant cavity of a 9 GHz EPR spectrometer, gave rise to EPR spectra of transient radicals. Oxime esters 1 supplied signals from both iminyl ArR\textsubscript{1}C=N\bullet and C-centered radicals R\textsubscript{2}\bullet. In this way, primary, secondary, and tertiary alkyl, allyl, and benzyl type radicals, and even product species from \sigma-radicals such as cyclopropyl, could be conveniently observed. C-Centered radicals had already been intensively studied by EPR, so we focused in on more exotic carbamoyl, N-centered, and O-centered radicals.

EPR spectra for an eclectic selection of iminyl radicals were obtained from photolyses of all the carbonyl oxime precursors 1–5. The spectra from ArCR\textsubscript{2}N\bullet were insensitive to the type of Ar ring or to the substituents in this ring and generally consisted of a simple 1:1:1 triplet with ~10 G splitting (see Table 1). Spectra from iminyls with \beta-H atoms, ArCH=N\bullet, such as the one shown in Figure 2a for radical 67 (Table 1), were particularly valuable because the large \alpha(H) of about 80 G left an uncluttered central window where spectra from other species could be

| Radical  | Structure | g-factor | hfs/G |
|----------|-----------|----------|-------|
| iminyl 67 | ![Iminyl 67](image) | 2.0034g | \(\alpha(N) = 10.0, \alpha(H) = 81.2, \alpha(2H) = 0.4\) G |
| iminyl 68 | ![Iminyl 68](image) | 2.0033g | \(\alpha(N) = 9.8, \alpha(2H) = 1.4, \alpha(3H) = 1.2\) G |
| carbamoyl | ![Carbamoyl](image) | 2.0017g | \(\alpha(N) = 21.8, \alpha(4H) = 0.7\) G |
| 21a | ![21a](image) | 2.0048g | \(\alpha(N) = 14.6, \alpha(4H) = 36.0\) G |
| aminyl 82 | ![Aminyl 82](image) | 2.0048g | \(\alpha(N) = 14.2, \alpha(2H) = 35.4, \alpha(2H) = 36.9\) G |
| phenoxyl | ![Phenoxyl](image) | 2.0049g | \(\alpha(1H) = 9.9, \alpha(2H) = 6.9, \alpha(2H) = 2.0\) G |
observed, unobscured by iminyl peaks, as illustrated in Figure 2a. Small hyperfine splittings (hfs) from H atoms in the Ar rings could occasionally be observed under high resolution (Figure 2a′ and Table 1). The spectra from dialkyliminyls often displayed additional fine structure from γ-H atoms, as in the spectrum from radical 68 (Figure 2b and Table 1). UV irradiations of carbonyl oximes 1, 2, 4, and 5 generated equal proportions of an iminyl radical and a second species, and therefore the iminyl spectra were extremely valuable as reference markers for assessing and monitoring the concentrations of other radicals.

The EPR parameters of iminyls implied that they were σ-type radicals with their unpaired electrons in orbitals centered on the N-atoms in the nodal plane of the C═N π-system. The DFT computed SOMO [B3LYP/6-311+G(2d,p)] for model radical 69 (R1 = Ph, R2 = Me) supports this conclusion (Figure 3). Delocalization of the unpaired electron into the ring π-system of aryliminyls is minor, and consequently ring substituents only exert weak effects on the reactivity of aryliminyls.

Although preparative chemistry based around iminyl radicals is well developed, quantitative data on the dynamics of individual processes is sparse. In the absence of reaction partners, iminyl radicals terminate rapidly by N to N coupling to give azines 70 (Scheme 13). The termination rate constants (2kₜ) for iminyls were measured from the decay curves of their EPR signals and found to be very large (Scheme 13). These large kₜ values signify that iminyl couplings of small to moderately sized species are diffusion controlled, just as are the terminations of small C-centered radicals.

Iminyls do undergo β-scissions to nitriles and alkyl radicals (Scheme 13); however, these dissociations are not important for aryliminyls or for iminyls with primary alkyl substituents at T ≲ 420 K. The only known rate constant for H-abstraction by an iminyl (6,6-diphenylhex-5-en-2-iminyl) was about a factor of 16 slower than for its C-centered analogue. This slow H-abstraction is crucial for the success of many N-heterocycle syntheses because ring closure is often in competition with H-abstraction.

Structure−activity relationships (SARs) for iminyl 5-exo-cyclizations provide a valuable resource for planning N-heterocycle syntheses. Extending from the one previously available data point, our EPR data provided such a SAR (Scheme 14). We generated a modest set of functionalized butenyl-iminyls 71a−f from oxime ester and dioxime oxalate precursors (Scheme 14). The EPR spectrum of iminyl 71a appeared as a triplet at 205 K (Figure 4, Im). As temperature was increased, its concentration decreased and that of the ring closed dihydropyrrolomethyl radical 72a increased (Figure 4, 260 K).

Similarly, all the iminyls 71a−f selectively ring closed in the 5-exo-mode, irrespective of the substitution pattern around the C═C double bond. Rate constants (kₗ) for the ring closures were determined from spectra like these by the usual steady-state kinetic EPR method (Scheme 14). The kₗ for phenylpentenyliminyl 71a was a factor of 25 less than kₗ for archetype C-centered hex-5-enyl radical cyclization. The main surprise in the SAR trend, as compared with hex-5-enyls, was that the 2,2-dimethyl-1-phenylpent-4-enyliminyl radical 71e ring closed more slowly than 71a showing a substantial inverse gem-dimethyl effect. DFT computations suggested sterical interaction of the Ph with the CMe₂ group pushed the aromatic ring out of conjugation with the plane of the imine moiety. To check on this, pentenyliminyls lacking this Ph substituent were needed. We were not able to study the simplest,
iminyln 75 selectively underwent the uncommon spiro-cyclization giving benzyl type radical 76.42 The rate constants shown in Scheme 14 were estimated from the EPR data and show the iminyln spiro process to be about an order of magnitude slower than for archetype C-centered radicals. Curiously, the product from 75 was benzofuroisouquinoline derivative 30a (Scheme 8), which implied ortho-radicals 77 as intermediates and appeared to conflict with the EPR result! The most likely explanation, which was supported by DFT computations, was that at the temperature of the preparative experiments (~100 K higher than the EPR study) the spiro-cyclization became reversible whereas the 6-ortho-process did not. Ortho-product 30a therefore accumulated because of thermodynamic control.

Photolyses of oxime oxalate amides yielded EPR spectra of carbamoyl radicals (A) along with iminyln radicals (I). Carbamoyl 21a ring closed in 5-exo mode even at 220 K to produce the N-benzylpyrrolidin-2-onylmethyl radical 22a (C), and Figure 5 is a remarkably clear “snapshot” of all three species at 220 K.

Figure 5. EPR spectra of PhCH=N• (I), carbamoyl 21a (A), and N-benzylpyrrolidin-2-onylmethyl radical 22a (C) at 220 K in t-BuPh solution. Black, experimental; red, computer simulation.

The EPR parameters of 21a and other carbamoyls indicate that they have considerable \( \sigma \)-character and are structurally akin to formyl and vinyl radicals (Table 1). The DFT computed SOMO for the model Me\(_2\)NC\(^•\)(\(\equiv\)O) (Figure 3) illustrates the sizable \( \sigma \)-orbital associated with the carbonyl C atom.

The \( k \) for the 5-exo cyclization of 21a, obtained by the steady state kinetic EPR method (Scheme 15), was slightly greater than the \( k \) for hex-5-enyl radical, as anticipated for a \( \sigma \)-radical and in view of the stabilizing amide group in the cyclized radical 22a. Carbamoyls 21c and 21f presented a unique opportunity to study the dynamics of \( \beta \)-lactam ring formation.21 The rate

Scheme 14. Dynamics of Ring Closures of Iminyl Radicals

| Scheme 14. Dynamics of Ring Closures of Iminyl Radicals |
|---|
| 2,2-dimethylpentenyliminyl, due to a competing process, but the radical containing a single Me substituent in the pentenyl chain, 71f, was successfully generated from an unsymmetrical dioxsime oxalate. The \( k \) for this species was a factor of 2.5 larger than \( k \) for 71a suggesting that the normal positive gem-dimethyl effect does operate for pentylenyliminyls lacking the aromatic substitutent at the C\(\equiv\)N bond. This is an intriguing example of a gem-dimethyl effect, which can be inverted by changing the substituent on the C atom adjacent to the CMe\(_2\) group from alkyl to aryl. Caution is obviously needed before making broad generalizations about CMe\(_2\) groups accelerating ring closure reactions!

Product analyses (see Schemes 4 and 5) implied that phenanthridinyl 74 was the main intermediate from iminyln radical ring closures onto aromatic acceptors. In an interesting contrast, EPR spectra obtained during photolyses of a benzofuran-containing oxime carbonate precursor showed that...
constants for their 4-exo ring closures onto C-C and C-NO bonds, respectively, exceeded that for 4-exo closure of pent-4-enyl type radicals but, of course, were smaller than those for 5-exo ring closures.

Oxime carbonates 4 and oxime carbamates 5 enabled the exotic and rarely encountered alkoxy carbonyloxyl 78 and carboxamoyloxyl radicals 79 to be investigated.23,28 The former species lose CO2 with release of alkoxy radicals R1O•,43 whereas the latter extrude CO2 with formation of aminyl radicals 82. DFT computations predicted that CO2 extrusion would become slower across the series MeCH2CO2• to EtNHCO2• to EtOCO2•. Furthermore, CO2 loss was computed to be slower for RNHCO2• than for R2NCO2• such that the former might have sufficient structural integrity for detection by EPR. The computed SOMOs demonstrate a dramatic contrast between MeCH2CO2•, which is confined mainly to the CO2 unit, and EtNHCO2• or EtOCO2•, with SOMOs delocalized to the adjacent heteroatoms and alkyl substituents (Figure 3). This was a further hint that monoalkyl RNHCO2• radicals might behave like EtOCO2• radicals in losing CO2 comparatively slowly.

O-Allyloxycarbonyloxyls 78 (R1 = allyl) cyclized in 5-exo-mode to dioxolan-2-onylmethyls 80, and kinetic EPR showed the rate to be nearly an order of magnitude faster than the archetype hex-5-enyl (Scheme 16). O-Benzylxycarbonyloxyl radicals 78 (R1 = Bn) selectively cyclized in the unusual spiro-mode to radicals 79, which were observable by EPR spectroscopy at temperatures below 270 K. Rate data for CO2 loss was obtained by kinetic EPR and showed this to be a remarkable 7 orders of magnitude slower than the analogous CO2 loss from EtCO2• radicals (Scheme 16)!

Rate and Arrhenius parameters were also obtained for benzylxycarbonyloxyl spiro-cyclizations.34 In conformity with the known high rates of alkoxy carbonyloxyl addition and abstraction reactions, kspiro for 78 (R1 = Bn) to 79 was greater than that of 4-phenylbutyl, the analogous C-centered radical.

The first evidence that N-monosubstituted carbamoyloxyl radicals 81 (R1 = H) had finite lifetimes was provided by the spectroscopic detection of the ring closed oxazolidin-2-onymethyl radical 83 at low temperatures.28 However, decarboxylation was rapid at room temperature for both N-, and N,N-disubstituted 81 such that they functioned as cleansources of aminyl radicals 82 (Scheme 16). The EPR spectral data (Table 1) and DFT computations (Figure 3) showed these aminyls to be π-type radicals reminiscent of secondary alkyl radicals. The 5-exo-ring closure of N-benzylpent-4-en-1-aminyl radical 82 to N-benzylpyrrolidin-2-ylmethyl 84 was also monitored by EPR spectroscopy and found to be comparatively slow (Scheme 16).

An assemblage of rate constants for 5-exo cyclizations [k5-exo (300 K)] of model N-, C-, and O-centered alkenyl type radicals demonstrates how this ring closure depends strongly on the nature of the radical-bearing atom (Figure 6). The rate constants span 5 orders of magnitude and fall neatly into three areas. N-Centered, including aminyl and iminyl, cyclize the slowest. C-Centered, including alkyl and acyl, cyclize at intermediate rates, and O-centered are fastest. Of course, k5 values outside the indicated ranges are possible for radicals containing dissimilar substituents. The rates are clearly not directly related to the electronegativities of the initial radical centers but probably reflect the reaction exothermicities.

Figure 6 neatly illustrates why C-radical chemistry has developed so much more fully. Rates of N-radical additions to C=C acceptors are slow, so room temperature preparative procedures are troublesome, C-radical rates are just right for rt protocols, and O-radical rates are suitable high, but competition from β-scission (CO2 loss or ketone formation) fiercely competes.

Scheme 16. Reaction Pathways and Rate Constants for Alkoxy carbonyloxyl and Carboxamoyloxyl Radicals

![Scheme 16](image-url)
8. CONCLUSION

Safe, easily handled precursors with long shelf-lives can be chosen from the above oxime derivative suite for a huge range of C-, N-, and O-centered radicals. The scope is obviously greatly extendable. These precursors lend themselves to green radical-mediated preparations of a great variety of allicycles and heterocycles. Both β- and γ-lactams can be conveniently obtained from suitably unsaturated amines via oxime oxalate amides. Currently methods for stereocontrol of the cyclization steps have not been investigated. The multiplicity of iminyl production from carbonyl compounds offer exceptional flexibility in the choice of either photochemical or MW-assisted routes for pyrrole, quinoline, and isoquinoline containing heterocyclic systems. O-Phenyl oxime ether Schiffbunds offer effective methodology for diaza-containing quinazoline production. The elegance of the EPR spectra pinpointed oxime derivatives as prime choices for structural and dynamic studies. By this means, mechanistic information even on the rapidly evolving alkoxycarbonyloxyl and carbamoyloxyl radicals was obtained. There is obvious scope for the development of synthetic protocols based around the alkoxyl and aminyl radicals that they produce at organic laboratory temperatures.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jcw@st-and.ac.uk. Tel: 44(0)1334 463864. Fax: 44(0)1334 463808.

Notes

The author declares no competing financial interest.

Biography

John C. Walton is Research Professor of Chemistry at the University of St. Andrews. He was born in St. Albans and was educated at Watford Grammar School and Sheffield University (B.Sc., D.Sc.), England. He joined the faculty of Dundee University in 1967 and moved to St. Andrews University (Ph.D.) in 1970, rising to full professor of chemistry in 1997 and becoming Research Professor of Chemistry in 2007. His early work was on structure—activity relationships for radical addition reactions and expanded to encompass applications of physical organic methods to organic mechanisms. He is known for EPR spectroscopic studies of delocalized radicals, for the discovery of an EPR method for conformational analysis of cyclic radicals, and for the first observations of strained cage radicals including cubyl. Recently he has developed “clean” radical-mediated synthetic protocols including (i) methods based on “pro-aromatic” cyclohexadienyl reagents, (ii) development of a suite of oxime derivatives for heterocycle syntheses, and (iii) photoseroxidation methods employing titanium dioxide and carboxylic acids.

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