Kinetic and Theoretical Study of 4-*exo* Ring Closures of Carbamoyl Radicals onto C═C and C═N Bonds
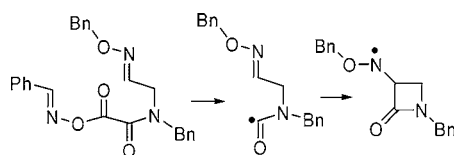
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ABSTRACT

Carbamoyl radicals were generated from oxime oxalate amides, and the kinetics of their 4-*exo* cyclizations onto C═C and C═NO bonds, leading to β-lactam-containing species, were studied by EPR spectroscopy. DFT computations with model carbamoyl radicals predicted 4-*exo* ring closures onto C═NO bonds to be facile, especially when *tert*-butyl substituents were present. The reverse ring-opening reactions were predicted to have much higher activation energies. Experimental evidence also favored slow reverse ring opening.

4-*exo* Cyclizations of 4-pentenyl type radicals are normally slow[1] and are opposed by the faster ring opening of the product cyclobutylalkyl radicals.[2] Cyclizations leading to four-membered ring azetidinones seem to differ from this norm because β-lactams have successfully been prepared via ring closures of carbamoyl radicals,[3−5] amidoalkyl radicals,[6] and amidyl radicals,[7] although yields were usually moderate. We showed recently that oxime oxalate amides, PhCH═NOC(O)C(O)NR₂, release carbamoyl radicals in photolyses sensitized with 4-methoxyacetophenone (MAP). Carbamoyl radicals with alkene groups appropriately sited in the NR₂

groups ring-closed to give pyrrolidinone or azetidinone rings, depending on the position of the double bond.[8] In a few instances, radical intermediates in these systems could be directly monitored by EPR spectroscopy, and this gave a unique opportunity to study, for the first time, the kinetics of ring closure to β-lactams.

Cyclization onto oxime ether functional groups is regiospecific to the C-atom of the C═N bond[9] and can be significantly faster than with analogous alkene acceptors.[10] Moreover, useful N-functionality remains available for further synthetic elaboration. We surmised that a carbamoyl

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radical with an oxime ether acceptor, 4-atoms removed from the radical center, would rapidly ring-close to an azetidinonylaminyl radical. Accordingly, we also prepared an oxime oxalate amide containing a BnOC=NCH₂− side chain (Bn = PhCH₂) and studied its photodissociation.

When a solution of benzaldehyde *O*-(*N*-benzyl-2-cyclohexenylaminooxalyl)oxime **1**, prepared as described previously,[8b] with MAP photosensitizer in *tert*-butylbenzene was photolyzed in the EPR resonant cavity at 220 K, the spectrum shown in Figure 1 was obtained. The set of six lines marked
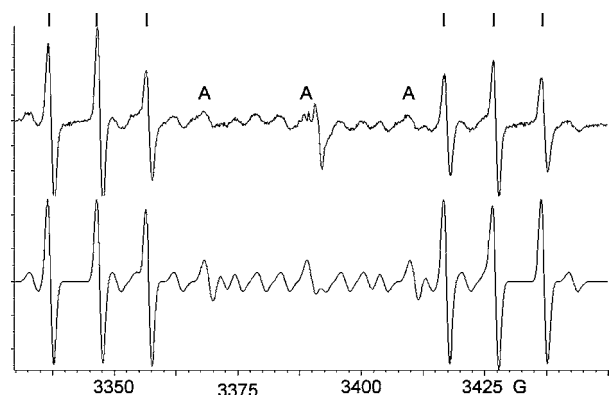

Figure 1. Top: EPR spectrum of radicals derived from **1** at 220 K in *tert*-butylbenzene. I = iminyl radical; **2**, A = aminoacyl (carbamoyl) radical **3**; other lines are from cyclized radical **4**. Bottom: computer simulation.

"I" are clearly due to the iminyl radical **2**,[11] and the three lines marked "A" are from the carbamoyl radical **3**.[8b] The *g*-factor of the third visible radical showed it to be C-centered (Table 1), and it was well simulated (Figure 1, bottom) by

Table 1. EPR Parameters of Azetidinone-Containing Radicals

radical	*T* (K) or theory[a]	*g*-factor	hfs (G)
4	220	2.0027	21.7 (H$_\alpha$), 41.5, 29.3, 16.8
4	DFT[a]		−21.7 (H$_\alpha$), 46.4 (H$_5$), 28.8 (H$_6$), 20.1 (H$_3$)
10	280	2.0049	13.7 (N), 13.7 (H), 2.5 (2H), 1.0 (2H)[b]
10	DFT[a]		11.6 (N), 18.5 (H$_\beta$), 1.5 (2H), −0.3 (2H$_4$)

[a] B3LYP/EPR-III//B3LYP/6-31G*; hfs not rotationally averaged. [b] Smallest hfs only partly resolved.

hfs from four nonequivalent H-atoms as listed in Table 1. These parameters are quite similar to those of the cyclohexyl radical in its locked conformation,[12] and they indicated that the third species was the cyclohexyl-type radical **4** from ring closure of radical **3**. This conclusion was supported by

density functional theory (DFT) computations,[13] which gave hfs in good agreement (Table 1). This is the first time a radical 4-*exo* cyclization has been spectroscopically observed.

Scheme 1. Ring Closure of 2-Cyclohexenyl Carbamoyl Radical Derived from an Oxime Oxalate Amide
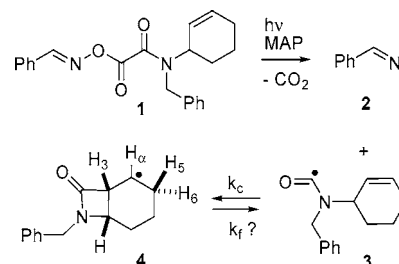
To probe the analogous ring closure onto a C=N bond, the oxime ether-substituted precursor **8** was first prepared. *O*-Benzyl hydroxylamine hydrochloride was condensed with chloroacetaldehyde to afford oxime ether **5**. The latter was reacted with benzylamine to provide amine **6**, which was converted to the oxime oxalate amide **8** by reaction with benzaldehyde *O*-(chlorooxalyl)oxime **7**.

The EPR spectrum obtained on photolysis of a solution of **8** and MAP in *tert*-butylbenzene at 220 K showed iminyl radical **2** together with carbamoyl radical **9** (*g* = 2.0018, *a*(N) = 23.2 G) and a weak spectrum of a third radical (see Figure 2). At higher temperatures, the spectrum of the third
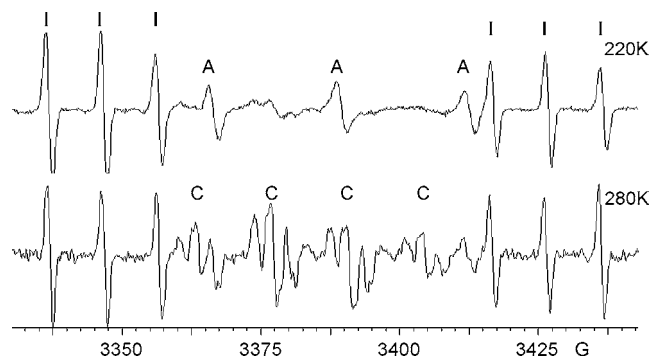

Figure 2. EPR spectra of radicals derived from **8** at 220 and 280 K in PhBu-*t*. I = iminyl **2**, A = carbamoyl **9**, C = aminyl **10**.

radical was stronger and found to have the parameters shown in Table 1.

The *g*-factor is typical of an alkoxyaminyl radical,[14] and the hfs of the *β*-H-atom (13.7 G) is of similar magnitude to that of cyclobutylmethyl,[15] the closest model four-membered-ring-containing radical reported. These parameters indicated

(11) Forrester, A. R.; Neugebauer, F. A. Landolt-Börnstein, *Magnetic Properties of Free Radicals*; Fischer, H., Hellwege, K.-H., Eds.; Springer-Verlag: Berlin, 1979; Vol. 9/cl, p 115−120.

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Scheme 2. Preparation of an Oxime Oxalate Amide with an Oxime Ether Side Chain and Formation of a Cyclized Oxyaminyl Radical
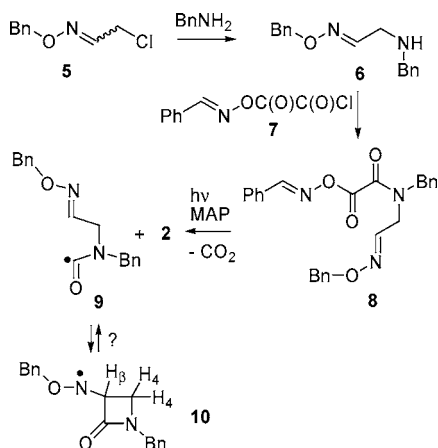
that the third species was the benzyloxyaminyl radical **10** from 4-*exo* ring closure of carbamoyl radical **9**. This conclusion was supported by a DFT computation that gave hfs in reasonable agreement (Table 1).

In assessing the dynamics of these ring closures, the reverse ring opening process (k_f) needs to be considered. Including this, it can easily be shown that:

$$[C] + [C]^2/[A] = k_c/2k_t - k_f/2k_t([C]/[A]) \qquad (1)$$

where A and C are the carbamoyl and cyclized radicals, respectively, and $2k_t$ is the rate constant for their termination reactions.[16,17a−c] In principle, a plot of the left-hand side of eq 1 vs [C]/[A] should give the two rate constant ratios as intercept and gradient. In practice, an experimental method of varying the radical concentrations is required. We varied the amount of MAP photosensitizer from 0.1 to 5 equiv and determined the radical concentrations using the EPR method.[18] For precursor **1**, this caused only about a doubling in the radical concentrations, and the effect was similar for **8**. For precursor **1** at 220 K, the change in [4]/[3] was only from 2.7 to 1.9 for MAP equivalents of 0.1 to 5, respectively. Plotting the data in the form required by eq 1 led to values of ca. 1×10^2 and 7×10^2 s^{-1} for k_f and k_c, respectively (see Supporting Information). However, because of the long extrapolation from a short data range, the error limits are particularly large. The results, therefore, can only be taken as an indication that the reverse ring opening is considerably slower than the cyclization at 220 K.

(15) (a) Kemball, M. L.; Walton, J. C.; Ingold, K. U. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1017−1023. (b) Ingold, K. U.; Maillard, B.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 2* **1981**, 970−974.

(16) Terminations of small radicals are fast, diffusion-controlled processes. Their rate constants are usually all the same when corrected for differences in solvent viscosity[17c] and are given by $2k_t$ for the *tert*-butyl radical.[17a,b]

(17) (a) Fischer, H.; Paul, H. *Acc. Chem. Res.* **1987**, *20*, 200−206. (b) Schuh, H.; Fischer, H. *Helv. Chim. Acta* **1978**, *61*, 2130−2164. (c) Maillard, B.; Walton, J. C. *J. Chem. Soc, Perkin Trans. 2* **1985**, 443−450.

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To gain further insight into the process, DFT computations[13] were carried out to determine the barrier heights of cyclization and ring opening for several carbamoyl radicals **11a−c**.

a; R=H, **b**; R=Me, **c**; R=Bu-*t*
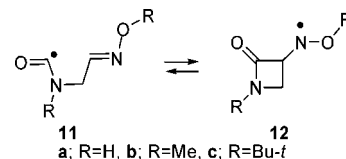
For the **11a → 12a** reaction, we were able to compare the results of several DFT approaches to those from QCISD-(T)/6-311G(2d,2p)//QCISD/6-31G*, the highest level of theory we could apply to this system. The benchmarking indicated that B3LYP/6-31+G** gave reasonable overall agreement with the correlated ab initio results (see Supporting Information). Thus, the forward and reverse barriers, along with the reaction energies for the **11 → 12** reactions, were computed using B3LYP/6-31+G**, and the results are reported in Table 2

Table 2. Computed Barriers for 4-*exo* Cyclizations of **11a−c** and Ring Openings of **12a−c** and Reaction Energies for **11 → 12**[a,b]

process	R = H **11a→12a**	R = Me **11b→12b**	R = *t*-Bu **11c→12c**
4-*exo* cyclization	9.2	7.2	4.8
ring opening	11.7	13.5	14.6
ΔE	−2.5	−6.3	−9.8

[a] Barrier heights and reaction energies do not include zero-point energies or enthalpy corrections. [b] Values in kcal mol^{-1}.

The calculations indicate that the 4-*exo* cyclizations onto oxime ether-type C=N bonds are exoergic with all substituents. The lengths of the newly formed C−C bonds in **12** are reduced from 1.59 Å (R = H) to 1.58 Å (R = Me) to 1.57 Å (R = *t*-Bu) and reflect the energetics of the reactions. These substituent effects are likely electronic in nature since steric constraints appear to be negligible in all three reactions. The barrier to cyclization decreases from **a** to **c**, a trend that is supported by the increases in the incipient C−C bond length in the transition state structures vis-á-vis 2.10 Å (R = H), 2.12 Å (R = Me), 2.13 Å (R = *t*-Bu). In parallel with this, the barrier to ring opening increases from **a** to **c**. The large difference in the forward and reverse barriers computed for the *tert*-butyl substituent indicate that ring opening would be negligible in the temperature range of the EPR experiments. By analogy, the same should be true for the benzyl-substituted species **9** to **10**. Therefore, the DFT computations support our conclusion of slow reverse reactions. They suggest, however, that for oxime ether-substituted carbamoyls with small N- and O-substituents (R = H, Me), ring opening could become important at higher temperatures.

Assuming that the reverse ring-opening reactions are negligible in the temperature range of the EPR experiments

(205−280 K), the right-hand term in eq 1 involving k_f may be neglected. The k_c values derived from the EPR concentration measurements of **3** and **4** and of **9** and **10**, when plotted in Arrhenius form for several different MAP concentrations, showed negligible dependence on MAP concentration (see Supporting Information). This supported our neglect of the RHS term in eq 1. The rate and Arrhenius parameters are listed in Table 3 along with data for some related processes.

Table 3. Rate and Arrhenius Parameters for 4-*exo* and 5-*exo* Cyclizations onto C=C and C=N Bonds

cyclization	$k_c(T)/s^{-1}$	$E_c{}^a$	$\log A_c{}^b$	ref
3 (4-*exo*)	5×10^4 (300)	7.3	10.1	c
9 (4-*exo*)	3×10^4 (300)	7.1	9.6	c
13 (4-*exo*)	2×10^4 (323)			1
14 (5-*exo*)	2.5×10^5 (298)	6.9	10.4	20
15 (5-*exo*)	4×10^7 (353)			21

^{a} Units of kcal mol^{-1}. ^{b} Units of s^{-1}. ^{c} This work.

The 4-*exo* cyclizations of **3** and **9** have slightly larger rate constants than the 4-*exo* cyclization of pent-4-enyl-type radical **13**, even though the latter is favored by a Thorpe−Ingold effect and produces a resonance-stabilized product radical. This confirms the supposition, referred to in the introduction, that cyclizations yielding azetidinone rings are faster than cyclizations giving cyclobutyl-type rings.
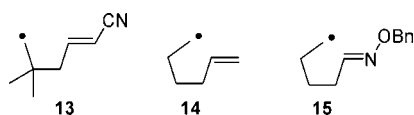
As expected, the 4-*exo* cyclizations of **3** and **9** have smaller rate constants than the 5-*exo* cyclizations of 5-hexenyl-type radicals **14** and **15**. The 5-*exo* cyclization of **15** onto a C=NO bond has a rate constant ca. 30 times larger than that of radical **14** at 353 K. Comparison of 6-*exo* cyclizations onto C=N and C=C bonds also shows the former to be faster.[10] In view of this, 4-*exo* cyclization onto a C=NO bond is expected to be faster than onto a C=C bond, although perhaps not by such a large factor.[19] The error limits are large on both sets of kinetic data so that although Table 3

shows that k_c for **3** (onto a C=C bond) is marginally greater than k_c for **9** (onto a C=NO bond), the two are the same within the error limits. The reason $k_c(\mathbf{3})$ and $k_c(\mathbf{9})$ are closer in magnitude than expected may be connected with the rather different structures involved in the two types of ring closure. Radical **3** is more rigid than radical **9** and cyclizes to give a bicyclic structure. Thus, the two processes are stereoelectronically somewhat dissimilar and general deductions are unsafe.

Oxime oxalate amides with alkene and oxime ether N-side chains photodissociate smoothly, under the influence of MAP, to yield iminyl and carbamoyl radicals. Spectroscopic observations of the carbamoyl radicals and their ring-closed product radicals enabled 4-*exo* cyclizations leading to β-lactam-containing species to be monitored for the first time. DFT computations with model carbamoyl radicals predicted 4-*exo* ring closures onto C=NO bonds to be facile, especially when *tert*-butyl substituents were present. The reverse ring-opening reactions were predicted to have much higher activation energies. Experimental evidence also favored slow reverse ring opening. Experimental rate constants for 4-*exo* ring closures of carbamoyl radicals onto C=C and C=NO bonds were found to be greater than those for 4-*exo* closure of 4-pentenyl-type radicals but smaller than those for 5-*exo* ring closures.

Supporting Information Available: General experimental and computational procedures, characterization for compounds **5**, **6**, and **8**, sample EPR spectra for radicals derived from **8**, tables of concentrations and kinetic data for radicals **3** and **9**, and computational data for radicals **11** and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) The k(C=N)/k(C=C) factor decreases from 6-*exo* to 5-*exo*; see ref 10.

(20) (a) Beckwith, A. L. J.; Easton, C. J.; Lawrence, T.; Serelis, A. K. *Aust. J. Chem.* **1983**, *36*, 545−556. (b) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron Lett.* **1985**, *26*, 373−376.

(21) Kim, S.; Joe, G. H.; Do, J. Y. *J. Am. Chem. Soc.* **1993**, *115*, 3328−3329.