First determination of the rate constant for ring-closure of an azahexenoyl radical: 6-aza-7-ethyl-5-hexenoyl[†]

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Competitive kinetic experiments utilising free radical carbonylation chemistry provide a first estimate for the rate constant for 6-*endo* cyclization of the 6-aza-7-ethyl-5-hexenoyl radical of $(4.8 \pm 2.4) \times 10^6 \text{ s}^{-1}$ at 90° C in benzene, in good agreement with ONIOM-G3(MP2)-CC+COSMO-RS calculations $(6.8 \times 10^6 \text{ s}^{-1})$.

It is now well established that radical carbonylation chemistry is useful for the construction of heterocycles. For example, one of us has shown that, unlike alkyl radicals, acyl radicals formed by the reaction of alkyl radicals with carbon monoxide are N-philic and react to form a variety of lactams (Scheme 1).^{1,2} These observations have been rationalised as being the result of multiorbital interactions that operate in the transition states for ringclosure in which the acyl radical is assisted by favorable orbital overlap with the nitrogen lone-pair.³

As part of this work we needed to determine kinetic data for these cyclization reactions and sought recourse to standard competitive kinetic experiments involving 1 and using tributyltin hydride as chain carrier (Scheme 2). In order to obtain a value for k_c , the rate constant for ring closure, Scheme 2, requires that both lactam 2 and aldehyde 3 are produced in quantities that can be detected by techniques such as gas





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† Electronic supplementary information (ESI) available: Fig. S1, derivation of eqn (3), experimental and computational details including the preparation of **6**, kinetic data and Gaussian Archive entries for **4**, **8** and **12**. See DOI: 10.1039/c0cc01262a



Scheme 2

chromatography (GC). Somewhat to our surprise, we were unable to detect aldehyde **3** under any of the conditions available to us (0.005–0.2 M Bu₃SnH, 90 °C, benzene) for conducting carbonylation experiments. One of the implications of this observation is that the rate constant for ring closure, k_c , is greater than about $4 \times 10^6 \text{ s}^{-1}$.‡

With this in mind it became clear that an alternative kinetic strategy was needed, one that did not require direct observation of 3. Close examination of Scheme 2 reveals that it should be possible to clock the rate of cyclization against the known rate constant, ${}^{4}k_{-CO}$, for decarbonylation of the acyl radical 4. Under pseudo first-order conditions in CO, rearrangement and integration of eqn (2) provides a function of unknown form (eqn (3)) in which the ratio of reduced product 2 to lactam 6 approaches the required ratio of rate constants $(k_{\rm c}/k_{\rm -CO})$ as the carbon monoxide concentration (or pressure, ρ (CO)) is extrapolated to zero.⁵ In other words extrapolation of a plot of [2]/[6] as a function $\rho(CO)$ to the intercept will provide an estimate of k_c . This analysis requires the establishment of an equilibrium between 4 and the initially formed radical 5, assumes a steady-state concentration of the radical 5 and that experiments are conducted with carbon monoxide not approaching zero concentration.†



Fig. 1 Dependence of $\ln([2]/[6])$ on carbon monoxide pressure, $\rho(CO)$.

The radical precursor **1** was prepared from 4-(phenylseleno)butyraldehyde⁶ as described previously.² Kinetic experiments were performed by dissolving **1** in benzene (1.0–2.0 mL) at the required concentration (0.017–0.056 M). Bu₃SnH (1.3 equiv.) and AIBN (few crystals) were added and the mixture charged with ten equivalents of CO (30–100 atm, 0.29–0.95 M)⁵ in an autoclave, followed by heating at 90 °C for one hour. Reaction mixtures were analysed directly by GC and products referenced against previously prepared samples of **2**² and **6**. Further details are available as part of the ESI.[†]

To our surprise, when plotted, [2]/[6] appeared to vary in an exponential fashion with CO pressure (ESI, Fig. S1)[†] and this was subsequently confirmed; indeed, $\ln([2]/[6])$ proved to be related linearly to CO pressure ($r^2 = 0.95$) (Fig. 1).

Inspection of Fig. 1 reveals that $\ln([2]/[6]) = -5.47$ (with a standard deviation of 0.5) when extrapolated to the (hypothetical) conditions of $\rho(CO) = 0$. Given that $k_{-CO} = 2.0 \times 10^4 \text{ s}^{-1}$ at 90 °C,⁴ with due precautions associated with the combination of kinetic data,⁴ one can provide a first estimate for k_c of $(4.8 \pm 2.4) \times 10^6 \text{ s}^{-1}$ at 90 °C.§



In order to provide further confidence in our rate data we also determined $k_{\rm c}$ using computational techniques. We have recently developed a G3-based version of the ONIOM procedure that can accurately model the energetics of larger radical reactions,⁷ and have shown that it can be used in conjunction with transition state theory to predict reliable rate data for radical ring-closure reactions,8 as well as a broad range of other radical processes.⁹ For the present work we use as our reaction core the corresponding cyclization of the parent imine 7, which we have studied previously in the gas phase.³ For use in the present work these previous calculations have been corrected to the G3(MP2)-CC//MP2/cc-pVDZ level of theory, and then combined with MP2/cc-pVTZ// MP2-cc-pVDZ calculations on the cyclization of 4, so as to obtain ONIOM-G3(MP2)-CC//MP2/cc-pVDZ energetics for this latter reaction.⁷ Since solvent effects are likely to be important, these were incorporated using COSMO-RS,¹⁰ which has been successful in our other recent studies of solvent sensitive systems.¹¹ Using this approach, our calculated rate coefficient for the cyclization of 4 in benzene at 90 °C is $6.8 \times 10^6 \text{ s}^{-1}$, in excellent agreement with experiment. The calculated logA and activation energy under these conditions are 9.6 and 29.3 kJ mol⁻¹ respectively. The MP2/cc-pVDZ optimised transition structure 8 for this reaction is provided in Fig. 2, full computational details are provided in the ESI.[†]



Fig. 2 MP2/cc-pVDZ optimised structure 8.

It is interesting to note that consistent with previous calculations involving the (Z)-isomer of 7 which is predicted to ringclose with a significantly higher barrier than its (E)-isomer,³ the (Z)-isomer of **4** is calculated to ring-close with a rate constant (k_c) of 7.4 × 10⁻³ s⁻¹ at 90 °C in benzene.†

It is instructive to compare the rate constant, k_c , for the cyclization of **4** (extrapolated to $4 \times 10^6 \text{ s}^{-1}$ at 80 °C)¶ with that for the ring-closure of the prototypical 5-hexenyl radical **9** (5-exo: $6 \times 10^5 \text{ s}^{-1}$ at 80 °C; 6-endo: $1 \times 10^4 \text{ s}^{-1}$)¹² and for 5-exo cyclization of an alkyl radical onto the imine moiety in radical **10** ($6 \times 10^6 \text{ s}^{-1}$ at 80 °C),¹³ Scheme 3. It is clear that orbital assistance during the 6-endo cyclization of **4** is responsible for a significant rate enhancement when compared to related systems.²

Buoyed by this excellent outcome, we turned our attention briefly to the cyclization of hydrazone **11**, another system for which no cyclization rate data appear to exist in the literature. Unlike imines, hydrazones such as **11** prefer to cyclize in the 5-*exo* manner (Scheme 4)¹⁴ and our previous calculations show that acyl radicals are not N-philic in their reactions with hydrazones.¹⁵ The MP2/cc-pVDZ transition state **12** for 5-*exo* cyclization of **11** is depicted in Fig. 3, full computational details are provided in the ESI.[†] ONIOM-G3(MP2)-CC+COSMO-RS calculations predict rate coefficients for the ring-closure of **11** to be 8.1 × 10^5 (5-*exo*) and 9.6 × 10^3 s⁻¹ (6-*endo*) at 80 °C in benzene. Preliminary kinetic studies using analogous methodology to that described in Scheme 2 provide a value of k_c of





Fig. 3 MP2/cc-pVDZ optimised structure 12.

 $1.2 \times 10^5 \text{ s}^{-1}$ (benzene, 80 °C) for the 5-*exo* mode of cyclization of **11**, in good agreement with our computational prediction.

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Notes and references

‡ Assuming a 5% GC detection limit and a value of $k_{\rm H}$ of about $10^6 \,{\rm M}^{-1}{\rm s}^{-1}$ as taken from ref. 3.

§ Errors expressed to one standard deviation.

- ¶ Assuming logA of approximately 9.5.
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