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5-Azahexenoyl radicals cyclize *via* nucleophilic addition to the acyl carbon rather than 5-*exo* homolytic addition at the imine

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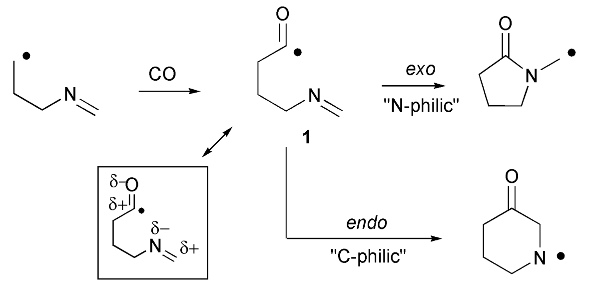
Molecular orbital calculations predict that the 5-azahexenoyl radical ring closes *via* nucleophilic addition to the acyl carbon to afford the 5-*exo* product; CCSD(T)/cc-pVDZ//BHLYP/cc-pVDZ calculations predict energy barriers of 36.1 and 46.9 kJ mol^{-1} for the *exo* and *endo* cyclization modes of the 5-azahexenoyl radical, respectively.

Radical cyclizations are important tools for the construction of various types of biologically active natural products and pharmaceuticals.[1] Many of these studies are concerned with cyclizations onto alkenes and to a lesser extent, onto alkynes and nitrogen containing multiple bonds.[2]

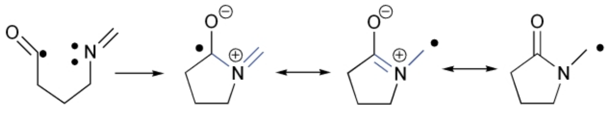
Recently, we explored acyl radical cyclizations onto imine groups.[3] Incorporation of the polar component created a new selective cyclization outcome where complete selectivity towards the *exo* product was achieved. The interpretation of this phenomenon is through the matching of partial charges, not seen in any of the previous examples. The acyl radical matches the δ−/δ+ character of the N=C acceptor double bond, creating an 'N-philic' acyl radical cyclization as seen in Scheme 1.



Scheme 1

The origin of this selectivity brings up intriguing mechanistic issues. It is well known that acyl radicals are considered nucleophilic in the context of addition to C=C double bonds containing electron-withdrawing groups.[4] With this in mind, the experimental observations seem contradictory because only products from attack of the acyl radical at the nucleophilic imine nitrogen are observed. In order to explain the observed regiochemistry in these reactions, two hypotheses have been considered.[3] Firstly, the 'C-philic' attack is the kinetic process followed by isomerization to the thermodynamically more stable *exo* radical. Alternatively, attack by the imine nitrogen at the carbonyl carbon gives rise to the *exo* radical directly (Scheme 2).

In order to understand the intimate details surrounding this highly regioselective cyclization process, we have examined the reaction pathways available to (**1**) by *ab initio* and density functional (DFT) techniques.



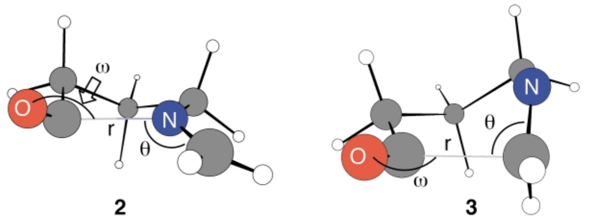
Scheme 2

Ab initio molecular orbital and DFT calculations were carried out using the Gaussian 98 program[5] using standard computational methods.[6]

Searching of the C_5H_8NO potential energy surface located structures (**2**, **3**) that proved to be stationary points at all levels of theory used in this study. Vibrational frequency analysis revealed that these structures correspond to the transition states for 5-*exo* and 6-*endo* ring closure of (**1**). Optimized structures are displayed in Fig.1, while calculated energy barriers are listed in Table 1.

Inspection of Fig 1 reveals that structure (**3**) resembles other 6-*endo* transition states in that the transition state distance (r) lies in the range 2.1–2.2Å and that attack angle (θ) is about 93° at all levels of theory in this study.[7,8] On the other hand, **2** appears to adopt a conformation in which the imine π-system is not orientated in a manner that allows the radical SOMO to overlap efficiently, rather it appears that the nitrogen lone-pair is predominantly directed toward the acyl carbonyl. It is interesting to note that the B3LYP method predicts transition states that are 'earlier' than those calculated using the other methods, consistent with the lower barriers ($\Delta E^{\ddagger}$) calculated using B3LYP optimized geometries (Table 1).

The data in Table 1 reveal that all levels of theory predict a preference for 5-*exo* cyclization, in agreement with experimental observation.[3] This preference is calculated to be 10 kJ mol^{-1} using CCSD(T)/aug-cc-pVDZ//MP2/aug-cc-pVDZ and 17–20 kJ mol^{-1} using B3LYP methods. The energy barrier ($\Delta E^{\ddagger}_{exo}$) associated with the *exo* reaction appears to converge to a value of about 44 kJ mol^{-1} using the MP2/aug-cc-pVDZ optimised geometry, while the analogous B3LYP data converged to a value of about 20 kJ mol^{-1}. The analogous barrier ($\Delta E^{\ddagger}_{endo}$) for the *endo* mode converges to 54 and 37 kJ mol^{-1} using the same methods, respectively. It is highly likely that the 'earlier' transition state predicted by B3LYP is responsible for these differences and, once again, highlights some of the



	5-*exo*			6-*endo*		
	r	θ	ω	r	θ	ω
UHF/6-311G**	1.816	124.7	117.2	2.188	93.1	121.8
MP2/aug-cc-pVDZ	1.789	121.3	113.4	2.106	92.4	118.9
B3LYP/cc-pVDZ	2.030	128.8	118.2	2.213	92.8	120.6
BHLYP/cc-pVDZ	1.916	126.6	117.1	2.179	93.4	121.9

Distances in Å; Angles in degrees.

Fig. 1 Optimized structures of transition states **2** and **3**.

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Table 1 Calculated energy barriers[a] ($\Delta E^\ddagger$) for the 5-*exo* and 6-*endo* modes of cyclization of **1** and imaginary frequency[b] associated with **2** and **3**

Method	$\Delta E^\ddagger_{exo}$	$\Delta E^\ddagger_{exo}$ + ZPE	ΔH_{exo}	ν (**2**)	$\Delta E^\ddagger_{endo}$	$\Delta E^\ddagger_{endo}$ + ZPE	$\Delta H^\ddagger_{endo}$	ν (**3**)
UHF/6-311G**	54.5	54.1	−125.3	305i	65.5	61.8	−76.9	331i
MP2/aug-cc-pVDZ	46.6	45.8	−118.5	501i	55.5	54.9	−46.8	628i
QCISD/aug-cc-pVDZ//MP2/aug-cc-pVDZ	44.3	—	−118.5	—	54.3	—	−46.9	—
CCSD(T)/aug-cc-pVDZ//MP2/aug-cc-pVDZ	43.8	—	−118.7	—	53.7	—	−46.7	—
B3LYP/cc-pVDZ	21.2	21.9	−129.5	352i	41.2	40.8	−56.0	465i
B3LYP/aug-cc-pVDZ//B3LYP/cc-pVDZ	20.5	—	−129.5	—	37.0	—	−55.3	—
QCISD/cc-pVDZ//B3LYP/cc-pVDZ	20.1	—	−129.3	—	36.9	—	−56.2	—
CCSD(T)/cc-pVDZ//B3LYP/cc-pVDZ	19.9	—	−129.4	—	36.5	—	−56.2	—
BHLYP/cc-pVDZ	39.8	39.1	−138.9	517i	52.2	51.1	−73.2	452i
BHLYP/aug-cc-pVDZ//BHLYP/cc-pVDZ	36.8	—	−140.2	—	47.6	—	−77.3	—
QCISD/cc-pVDZ//BHLYP/cc-pVDZ	36.3	—	−140.3	—	47.1	—	−77.5	—
CCSD(T)/cc-pVDZ//BHLYP/cc-pVDZ	36.1	—	−140.5	—	46.9	—	−78.0	—

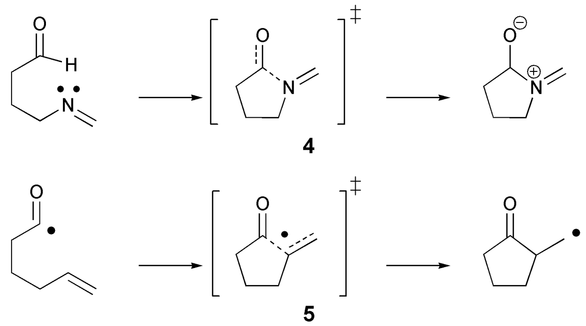
[a] Energies in kJ mol^{-1}. [b] Frequencies in cm^{-1}.

difficulties encountered in the application of B3LYP to radical transition state calculations involving acyl radicals.[9]

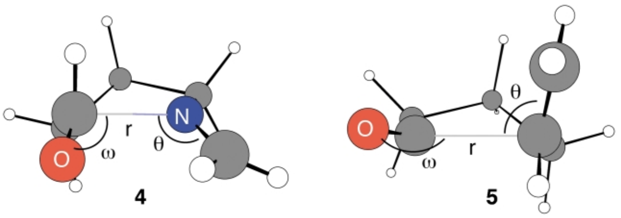
There is growing evidence to suggest that the BHLYP (BHandHLYP) method is a superior density functional method for application to radical systems.[10] The structural and thermodynamic data presented above reinforce this view, with BHLYP transition state geometries for **2** and **3** in closer agreement with the MP2-generated data. The energy barriers calculated using the BHLYP/cc-pVDZ geometries converge to about 36 and 47 kJ mol^{-1} for the *exo* and *endo* reactions, respectively.

In order to provide further evidence for the nucleophilic nature of the 5-*exo* reaction, we chose to locate the transition states for the 5-*exo* ring closure of 5-aza-5-hexenal and the 6-hexenoyl radical; systems in which there is no mechanistic uncertainty (Scheme 3).

Fig 2 displays the optimised geometries of the transition states (**4**, **5**) involved in the 5-*exo* ring closures depicted in Scheme 3.



Scheme 3



4 **5**

	nucleophilic			radical		
	r	θ	ω	r	θ	ω
MP2/aug-cc-pVDZ	1.750	122.0	89.9	2.210	108.1	122.1
B3LYP/cc-pVDZ	2.000	122.4	91.7	2.220	104.5	127.3
BHLYP/cc-pVDZ	2.000	122.6	91.5	2.220	104.7	127.2

Distances in Å; Angles in degrees.

Fig. 2 Optimized structures of transition states **4** and **5**.

The data provided clearly show that, apart from conformational differences, the transition state (**2**) calculated to be involved in the 5-*exo* cyclization of the 5-azahexenoyl radical (**1**) more closely resembles **4** rather than **5** at all levels of theory used. Indeed, as expected, **4** is arranged such that the nitrogen lone-pair is oriented toward the aldehyde carbonyl carbon, while **5** resembles a typical 5-*exo* transition state in which the olefinic π-system is well aligned for overlap with the acyl radical SOMO, and is in good agreement with previous calculations.[8] We conclude therefore, that the 5-azahexenoyl radical (**1**) cyclizes preferentially in the 5-*exo* mode by nucleophilic attack of the nitrogen lone-pair at the acyl carbon.

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