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Kinetic and thermodynamic factors in the regioselectivity of α-carboallyloxymethyl radical cyclizations. A computational study†

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Ab initio transition-state modeling of α-carboallyloxymethyl radical (**1**) demonstrates not only that 6-*endo* cyclization is kinetically disfavored by an overwhelming margin, but that the 5-*exo* educt radical (**2**) is also thermodynamically favored over the 6-*endo* educt radical (**3**). This may account for the absence of any examples of 6-*endo* cyclization of any *N*-allylic α-carbamoylalkyl or *O*-allylic α-carbalkoxyalkyl radical congeners of **1** in the literature.

Introduction

During the preparation of a review[1] on syntheses of lactams and lactones by carbon–carbon bond forming radical cyclizations which included ones of the type depicted in Scheme 1, a thorough search of the literature from 1967 through to 2004 found no unambiguous reports of 6-*endo* cyclization of *N*-allylic α-carbamoylalkyl radicals or *O*-allylic α-carbalkoxyalkyl radicals. This statement includes the qualification "unambiguous" because among the one hundred plus articles researched describing cyclizations of allylic ester or amide congeners of **1**, two instances were uncovered suggesting that such 6-*endo* cyclizations had taken place. The first,[2] by Nagashima and co-workers, has since been proven[3] to be a case of an erroneous structural assignment to the 12-membered dilactone product, and no 6-*endo* product was actually formed. The second,[4] by Yamamoto and co-workers, is better accounted for as a tandem 5-*exo*/3-*exo* cyclization of an *O*-allylic α-acrylate radical followed by internal ring opening of the resultant bicyclo [3.1.0] radical, leading to the same product as would have been formed by direct 6-*endo* cyclization of the substrate. Experimental evidence has ruled out the direct 6-*endo* path, and confirmed the tandem cyclization mechanism.[5] Since no other reports of 6-*endo* cyclizations of the type depicted in Scheme 1 could be found, it seemed worthwhile to investigate the possible causes underlying this surprising lacuna.[6] *Ab initio* computations were seen as a means of elucidating the kinetic and thermodynamic factors directing the cyclization of radicals such as **1** to better understand the reasons, if any, for the apparent exclusivity of the 5-*exo* pathway.

When the same reactant can lead to two different transition-state structures, their relative energies can be used to estimate the relative rates of the competing reaction pathways. Computational models can provide relative enthalpies for transition-state structures. If the assumption is made that the entropies of activation are very nearly the same, it then becomes possible to derive from the Arrhenius equation a simplified expression (1) (see below) for the relative rates of the competing pathways as a function of the difference in enthalpies of the transition-state structures. In the case of 5-*exo* cyclization *vs.* 6-*endo* cyclization, the assumption that $\Delta S^{\ddagger}_{5x} \approx \Delta S^{\ddagger}_{6n}$ does not seem intuitively unreasonable, but these results must be so qualified.

Results and discussion

The molecular modeling suite used‡[7] includes an algorithm for locating an optimized transition-state geometry (saddle-point) beginning from either reactants or products. A UHF/3-21G$^{(*)}$ Monte Carlo search identified fourteen possible conformational minima for acyclic radical **1**, but only two for γ-lactone radical **2** (*ax*/*eq* –$CH_2^{\bullet}$), and just one for δ-lactone radical **3**. Consequently, it seemed the least ambiguous approach to finding reasonable transition-state geometries was to begin with the cyclic radicals and break the appropriate ring bonds. Because the axial and equatorial conformations of **2** might well lead to distinct transition-states, a possible transition-state structure was created from both, and from δ-lactone radical **3**, as well. Optimization at the UHF/6-21G* level did produce three distinct transition-state geometries, Fig. 1, and these were used as the starting points for UMP2(FC)/6-31G* transition-state geometry optimizations.[8] Frequency calculations confirmed that each has only one imaginary vibrational mode, corresponding to bond formation. Finally, UMP2(FC)/6-311G+** single-point energies were computed for those structures. The 5-*exo* transition-state leading to cyclic radical *eq*-**2** is the lowest in energy. The 5-*exo* transition-state leading to educt radical *ax*-**2** is 14 kJ mol^{-1} higher, and the 6-*endo* transition-state leading to radical **3** is 31 kJ mol^{-1} higher. Substitution of these values into eqn. (1) gives a kinetic ratio for 5-*exo* to 6-*endo* cyclization of 300 000 to 1 at room temperature, 42 000 to 1 at 80 °C, and 9000 to 1 at 140 °C. Because C–C bond forming radical additions are quite exothermic, 5-*exo* and 6-*endo* cyclizations of this type are nearly always irreversible, *i.e.*, under kinetic control. The predicted relative rates are consistent with no trace of 6-*endo* products ever being detected.

$$k_1/k_2 = \exp[(\Delta H^{\ddagger}_2 - \Delta H^{\ddagger}_1)/RT] \qquad (1)$$

Closer inspection of the three transition-states reveals structural features that are entirely consistent with the computed relative energies. It is accepted[9] that the optimum angle for the approach of the radical to the π-bond, Fig. 2, is approximately

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† Electronic supplementary information (ESI) available: Cartesian coordinates and computed total energies for all structures reported plus vibrational frequencies of transition-state structures. See http://www.rsc.org/suppdata/nj/b4/b418257j/

‡ All computations were performed with Spartan '04 for Macintosh version 1.0.1 on an Apple G5 PowerMac 1.8 GHz dual processor desktop.

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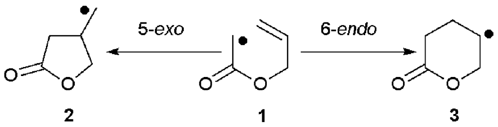

Scheme 1

109°. In the transition-state leading to the equatorial conformation of **2** this angle is 109°, and in the transition-state leading to the axial conformation of **2** this angle is 110°, both nearly ideal. In contrast, in the transition-state leading to the 6-*endo* product, the radical is forced to approach the terminus of the π-bond at an angle of 91°, much farther from the ideal. The optimum direction for approach of the radical is also directly along the axis of the π-bond, Fig. 3(a). For the 5-*exo* cyclizations, the transition-state leading to the equatorial conformation of educt **2** requires the approaching radical center to be off-axis by 5.5°, and the transition-state leading to the axial conformation of educt **2** permits approach of the radical center from only 2.3° off-axis. In contrast, the 6-*endo* transition-state constrains the radical center to approach the π-bond from 19° off-axis, Fig. 3(b). Comparison of inter-atomic distances is also revealing. For the 5-*exo* transition-state leading to the *ax*-**2** educt, the distance between the radical center and the internal carbon of the π-bond is 2.203 Å, while in the 6-*endo* transition-state the distance from the carbon radical to the terminus of the π-bond is 2.236 Å. This correlates to the 6-*endo* transition-state being less "product-like" and hence, for an exothermic reaction, higher in energy.

In order to test the "reasonable-ness" of the transition-states, each of the three saddle-point structures was subjected to geometry optimization at the UHF/6-31G* level, in order to find the local (*E*)-conformational minima of acyclic radical **1** which most resembled each transition-state. Both the 6-*endo* transition-state and the 5-*exo* axial transition-state converged to one and the same local minimum of radical **1**, while the 5-*exo* equatorial transition-state produced a different conformational minimum (Fig. 4). Subsequent UMP2(FC)/6-31G* geometry optimizations followed by UMP2(FC)/6-311G+** single-point energy calculations of these radicals showed the (*E*)-conformational minimum of radical **1** leading to the *eq*-**2** transition-state to be 2.2 kJ higher in energy than the (*E*)-**1** minimum leading to the *ax*-**2** transition-state. To test whether the molecule would progress smoothly from these corresponding acyclic minima to the proposed transition-states, for each of the two local minima of radical **1** thus obtained, the distance between the acyclic radical center and the appropriate terminus of the double bond was constrained and incremented in five steps until it equaled the C–C distance of the forming bond in the corresponding transition-state. Each of the intermediate structures thus generated was then subjected to geometry optimization at the UMP2(FC)/6-31G* level of theory. Visual comparison of all the intermediary structures confirmed that the internal geometries of these local minima progressed to the internal geometries of the corresponding transition-states in a smooth manner, with no discontinuous jumps. This cannot be said to prove the absolute accuracy of the calculated relative energies of the proposed transition-states, but it does demonstrate an internal consistency to the models.

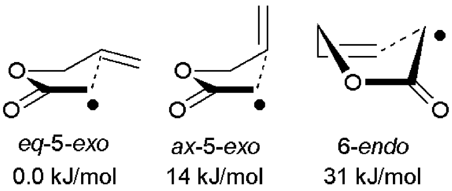

Fig. 1 Relative energies of cyclization transition-states.

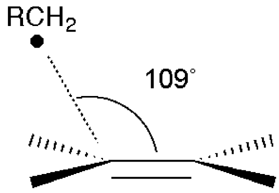

Fig. 2 Optimum angle of radical approach to a π-bond.

In an attempt to model the reaction energy profile completely, the global minimum (*Z*)-conformation of radical **1** was taken from the earlier Monte Carlo search, and subjected to a UMP2(FC)/6-31G* geometry optimization followed by a UMP2(FC)/6-311+G** single-point energy calculation. Next, the value of 64 kJ mol^{-1} for the barrier for OC–O rotation was obtained by beginning with the global minimum (*Z*)-conformation of radical **1** and manually setting the O═C–O–CH$_2$ torsional angle to 90°, then performing a UMP2(FC)/6-311+G** single-point calculation on that structure. This method has been demonstrated to be accurate[10] for computing the corresponding rotational barriers of analogous amide radicals where direct experimental data is available,[11] and falls within the range of literature values for the experimentally determined barriers to OC–O rotations of a variety of esters.[12] Finally, geometry optimizations of cyclic radicals *eq*-**2**, *ax*-**2** and **3** were carried out at the UMP2(FC)/6-31G* level of theory, and a UMP2(FC)/6-311+G** single-point energy was computed on each of those structures. As might be expected, γ-lactone radical **2** with the radical methyl group oriented equatorially is slightly more stable (3.1 kJ mol^{-1}) than the conformation with the radical methyl group oriented axially. Perhaps surprisingly, the single conformational minimum of δ-lactone radical **3** turned out to be higher in energy than either conformation of radical **2** (6.1 kJ mol^{-1} relative to *eq*-**2**). This difference in would give a thermodynamic product distribution of 92 to 8 in favor of the 5-*exo* product (at 25 °C). This result was not entirely unexpected, because cyclizations of congeners of **1** possessing two radical stabilizing groups on the acyclic radical center, under conditions which could allow for reversible ring closure (slow quenching of cyclized radical), *i.e.*, reactions at least partially under thermodynamic control, still produced no detectable amounts of 6-*endo* products.[13] It may be argued that the differences between the calculated energies of the three educt radicals are so small as to be within the margin of error of the computational methods used, but a considerable body of experimental observations and these modeling results are mutually supportive.

These results, which indicate that the rotational barrier between (*Z*)-**1** (unable to cyclize) and (*E*)-**1** (able to cyclize) is larger than the barrier to 5-*exo* cyclization of (*E*)-**1** itself (64 kJ mol^{-1} *vs.* 48 kJ mol^{-1}), are entirely consistent with experimental observations on the temperature dependence of such cyclizations,[14] as well. For example, while *N*-allyl-*N*-methyliodoacetamide and *N,N*-diallyliodoacetamide both cyclize rapidly and efficiently at 80 °C, the latter also cyclizes quantita-

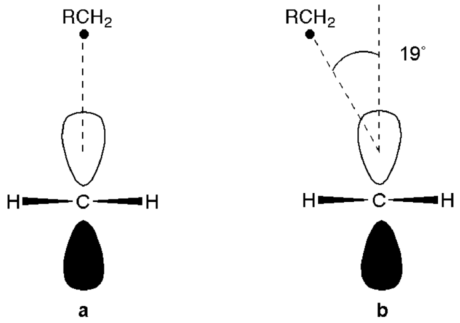

Fig. 3 Optimum direction of radical approach to a π-bond.

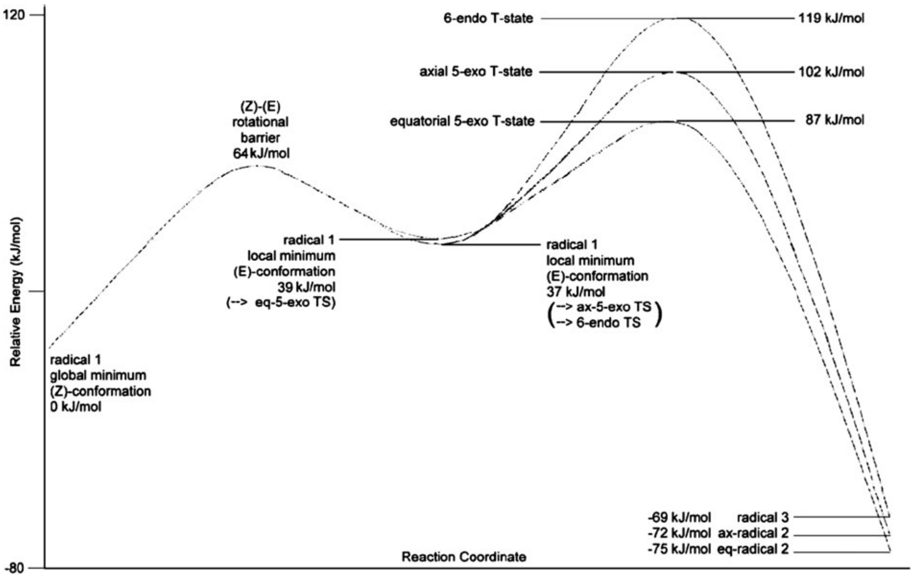

Fig. 4 Reaction energy profiles for 5-*exo* and 6-*endo* cyclizations of π-carboallyloxymethyl radical (**1**).

tively at 25 °C, while the former gives only <50% yield at room temperature. This serves as an independent corroboration of the self-consistency and accuracy of the computations.

Conclusions

Computational modeling of the transition-states and the educt radicals from the 5-*exo* and 6-*endo* cyclizations of the prototypical α-carboallyloxymethyl radical at levels of theory appropriate to correctly order them by internal energy strongly supports the contention that it is extremely unlikely that 6-*endo* cyclizations of this type will be observed,[15] because they are not only overwhelmingly disfavored kinetically, but disfavored thermodynamically, as well.

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15 It may be worth noting that these computations are for isolated molecules in the gaseous phase, while reactions of this type are typically carried out in solution. Although aggregate inter-molecular interactions and solvent effects could potentially have an influence on the relative stabilities of the species discussed here, radical reactions are well known to be fairly insensitive to such effects (ref. 6*k*). On the other hand, such interactions are also well known to exert a significant effect on the (*Z*)–(*E*) rotational barriers of esters and amides (ref. 12*a*). This, in turn, can influence the rates of reactions which require such a rotation to achieve the desired transition-state, even if the reaction itself is otherwise insensitive to solvent effects. For an example, see: M. E. Jung and J. Gervay, *J. Am. Chem. Soc*., 1989, **111**, 5469.