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Intramolecular Oxyallyl–Carbonyl (3+2) Cycloadditions

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Abstract

Cycloadditions involving oxyallyl intermediates typically require an electron-rich diene or alkene, but we have discovered the first examples of the cycloaddition of heteroatom-stabilized oxyallyls onto carbonyl groups. An oxazolidinone-substituted oxyallyl undergoes chemoselective (3+2) cycloaddition onto the carbonyl group of a tethered dienone, in preference to formation of the expected (4+3) cycloadduct. Density functional theory calculations indicate that the (3+2) cycloaddition takes place through a concerted, highly asynchronous mechanism. The transition state features simultaneous interactions of the oxyallyl LUMO with the carbonyl π and lone pair orbitals, which place this reaction halfway between a purely pericyclic and a purely pseudopericyclic process (“hemipseudopericyclic”). Further (3+2) cycloadditions involving tethered phenylketones and a tethered enone were predicted theoretically and verified experimentally.

Oxyallyl cations (**1**, Scheme 1) are valuable substrates for cycloaddition reactions that provide access to a variety of ring types.¹ Both $[4\pi+2\pi]$ and $[2\pi+2\pi]$ modes of cycloaddition are known under thermal conditions.² Important examples are, respectively, the (4+3) cycloadditions with dienes that lead to cycloheptenones and the (3+2) cycloadditions with alkenes that lead to cyclopentanones. A frequent hallmark of oxyallyl cycloaddition chemistry is a requirement for an electron-rich partner (diene or alkene), since the oxyallyl cation is electrophilic. These polar cycloadditions often have stepwise mechanisms.³ We have now uncovered an unprecedented type of oxyallyl cycloaddition that displays the opposite features: a concerted intramolecular (3+2) cycloaddition of an oxazolidinone-substituted oxyallyl onto the carbonyl group of a dienone, enone, or phenyl ketone. While (3+2) cycloadditions have been reported for oxyallyls generated from α , α' -dibromoketones,^{4–6} to the best of our knowledge, such (3+2) cycloadditions involving heteroatom-stabilized oxyallyls have not been reported before.

Over recent years, we have explored (4+3) cycloadditions of oxazolidinone-substituted oxyallyls (**3**, Scheme 2) with numerous classes of dienes.⁷ Oxyallyls **3** are readily generated by oxidation of allenamides and can be trapped either intermolecularly or intramolecularly by dienes. We had intended to apply the allenamide oxidation/(4+3) cycloaddition sequence

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ASSOCIATED CONTENT

Supporting Information. Experimental procedures, compound characterizations, NMR spectra, X-ray structural files, computational methodology and data, and complete citations for ref. 9. This material is available free of charge via the Internet at <http://pubs.acs.org>.

to access bicyclic species **4c** (Figure 1), in a planned synthesis of aromadendrane natural products.⁸ Unexpectedly, treatment of allenamide **2c** with DMDO under standard conditions led not to **4c** but to an oxabicyclic species, **5c** (85%), whose identity was confirmed by X-ray crystallography. Adduct **5c** is the product of chemoselective (3+2) cycloaddition of the oxyallyl onto the carbonyl group of the tethered dienone.

The formation of **5c** is surprising, given that other oxyallyls in which the diene is connected by a 3-carbon tether do undergo intramolecular (4+3) cycloadditions (e.g. Scheme 2b).^{2c} We conducted density functional theory calculations to explore how **5c** is formed.⁹ Transition states were computed for the (4+3) and (3+2) cycloadditions of **3c** leading to **4c** and **5c**, respectively, at the B3LYP/6-31G (d) level of theory.¹⁰ Activation energies were then computed from M06-2X/6-311+G (d, p) single-point calculations,¹¹ and solvent effects (CH₂Cl₂) were modeled through SMD calculations.¹² The computational results are shown in Figure 2. For comparison, we also computed transition states for intermolecular cycloadditions of a model oxyallyl (**3d**) with hexadienone (Figure 3).

The activation energies for the intermolecular cycloadditions (Figure 3) show that the dienone has no innate preference for the (3+2) mode of cycloaddition. The (3+2) transition state (**TSD**) is 12.4 kcal/mol higher in energy than the (4+3) transition state (**TSC**) in the gas phase ($\Delta\Delta G^\ddagger$), and 6.4 kcal/mol higher in solution. By contrast, the intramolecular (3+2) cycloaddition of **3c** (Figure 2) is favored over (4+3) cycloaddition by 7.7 kcal/mol in the gas phase and by 13.7 kcal/mol in solution. Both of these modes of intramolecular cycloaddition are downhill by more than 40 kcal/mol (ΔG_{soln}). The switch in chemoselectivity displayed by **3c** reflects a 4.6 kcal/mol lower activation enthalpy and a 3.1 kcal/mol smaller entropic term ($-T\Delta S^\ddagger$). While the inter- and intramolecular (3+2) TSs are geometrically very similar (except in the orientation of the diene chain), the (4+3) transition state occurs intramolecularly at a more advanced stage of bond formation and the carbonyl group is twisted 21° out of the diene plane (compared with 7° in **TSC**).

The (3+2) cycloadditions are concerted but highly asynchronous processes. C–O bond formation is much more advanced at the TS (1.87 Å) than C–C bond formation (3.11–3.15 Å). Addition is antarafacial with respect to **3c** or **3d** and suprafacial with respect to the carbonyl, in agreement with the orbital symmetry rules for a thermal $[2\pi+2\pi]$ cycloaddition.¹³ To explore the details of the mechanism, we calculated transition states for alternative modes of (3+2) cycloaddition in the reaction of **3d** with formaldehyde (Figure 4). The preference for antarafacial addition over suprafacial addition (**TSE** vs **TSF**) is 3 kcal/mol. The concerted antarafacial mechanism is favored by at least 10 kcal/mol over stepwise mechanisms. The HOMO and LUMO of oxyallyls **3** are depicted at the bottom of Figure 4. The HOMO is enolate-like, while the LUMO has both allyl π^* and iminium π^* character.¹⁴ To reach the antarafacial transition state, the iminium and enolate moieties rotate into a roughly perpendicular arrangement that allows maximum overlap with the π orbitals of the carbonyl. Orbital interactions with π (C=O) and π^* (C=O), which define the pericyclic $[2\pi+2\pi]$ cycloaddition, are accompanied by a simultaneous interaction between the LUMO of **3** and a carbonyl oxygen lone pair. The latter interaction endows the reaction with pseudopericyclic¹⁵ character. The degrees to which pericyclic and pseudopericyclic character contribute in **TSE** are evident in the geometry of approach by the aldehyde when viewed along the C=O bond (Figure 4), and are approximately equal. The iminium terminus of **3d** approaches at an angle of 47° with respect to the CH₂=O plane, halfway between the angles expected for purely pericyclic (90°) and pseudopericyclic (0°) processes. We describe this new type of reaction not as pericyclic or pseudopericyclic, but as “hemipseudopericyclic”.

We also explored the feasibility of intermolecular (3+2) cycloadditions. Reactions of **3d** with ketones, esters, and aliphatic or aromatic aldehydes are predicted to have $\Delta H^\ddagger = 6-9$ kcal/mol and $\Delta G^\ddagger_{\text{soln}} = 20-23$ kcal/mol¹⁶ (see the Supporting Information). Unfortunately, experimental attempts to perform intermolecular (3+2) cycloadditions with a number of carbonyl systems including aldehydes, ketones, esters, and amides were thwarted by competing oxidation of the carbonyl substrates under the conditions used for generation of the oxyallyl. Intramolecularity appears necessary to allow cycloaddition to compete with these unwanted oxidation reactions.¹⁷ Consistent with this, analogous (3+2) cycloadditions were accomplished with tethered phenyl ketones **2e-g** and the tethered enone **2h** (Scheme 3). On the other hand, methyl ketone **2i** failed to react under the same conditions. An electron-rich carbonyl substituent (R) appears necessary to stabilize the cation-like character at the carbonyl carbon in the highly asynchronous transition state. Calculations for **2e-2i** agree with experiment, predicting the methyl ketone to have a barrier 2 kcal/mol higher than that of **2c**, while the vinyl and phenyl ketones have lower barriers that decrease as the ketone becomes more electron-rich.

The (3+2) cycloadditions of **3** with carbonyl compounds are an unexpected addition to the repertoire of oxyallyl reactivity.⁴⁻⁶ Oxyallyls **3** possess a reactivity profile quite different from most other synthetically-important oxyallyls, which are cationic, electrophilic species. We had previously reported that oxyallyls **3** are ambiphilic in (4+3) cycloadditions with furans.^{14b} The cycloadditions onto carbonyls represent an even more unusual pairing and suggests tantalizing new synthetic prospects, and pursuit of potential applications is underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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16. Amides are predicted to be more reactive than these types of carbonyl compounds. For example, cycloaddition of **3d** with dimethylacetamide is calculated to have $\Delta H^\ddagger = 1.0$ kcal/mol and $\Delta G^\ddagger_{\text{soln}} = 12.1$ kcal/mol.

17. We also located a transition state for an alternative mode of (3+2) cycloaddition in which the formaldehyde carbon binds to the oxyallyl oxygen rather than to the oxyallyl carbon, leading to a 4-alkylidene-5-oxazolidinyl-1,3-dioxolane. This transition state is much lower in energy than **TSE** ($\Delta G^\ddagger = 10.7$ kcal/mol) and may represent an unwanted side reaction in certain of our attempted intermolecular cycloadditions; however, its importance depends on the carbonyl substituents. With hexadienone, for example, addition across CCO is 0.2 kcal/mol higher in energy than addition across CCC. At this stage, we have not observed any products that could be assigned to cycloadditions of ketones across CCO of oxyallyls. In all of our intramolecular examples, addition across CCO is prevented by the geometrical constraints of the tether. Analogous products have been reported from α,α' -dibromoketones and ketones or amides under reductive conditions: see ref. 4e,f

Figure 1.
Synthesis and X-ray crystal structure of the (3+2) cycloadduct **5c**.

TSA

(4+3)

$$\Delta H^\ddagger = 9.2$$

$$[\Delta G^\ddagger = 14.3]$$

$$(\Delta G^\ddagger_{\text{soln}} = 17.3)$$

TSB

(3+2)

$$4.6$$

$$[6.6]$$

$$(3.6)$$

Figure 2.

Transition states for intramolecular (4+3) and (3+2) cycloadditions of **3c** that lead to **4c** and **5c**, respectively. Distances in Å, $\Delta H^\ddagger$ and $\Delta G^\ddagger$ in kcal/mol (M06-2X//B3LYP, SMD solvation in CH_2Cl_2).

Figure 3.
Transition states for intermolecular (4+3) and (3+2) cycloadditions of oxyallyl **3d** with hexadienone.

Figure 4. Transition states for antarafacial and suprafacial (3+2) cycloadditions of oxyallyl **3d** with formaldehyde.

Scheme 1.
Generalized (4+3) and (3+2) Cycloadditions of Oxyallyl Cations

Scheme 2.

Intermolecular and Intramolecular (4+3) Cycloadditions of Allenamide-Derived Oxazolidinone-Substituted Oxyallyls with Dienes^{7a,c}

	R	Time	Yield	$\Delta H_{\text{calc}}^\ddagger$	$\Delta G_{\text{calc}}^\ddagger$
2e	<i>p</i> -C ₆ H ₄ OMe	40 min	82%	3.5	5.0
2f	Ph	40 min	84%	4.8	6.8
2g	<i>p</i> -C ₆ H ₄ F	1.5 h	70%	5.2	7.2
2h	vinyl	3.5 h	64%	6.0	7.7
2i	Me	3.5 h	0%	6.8	8.9

Scheme 3.

Experimental and Theoretical Investigations of Other (3+2) Cycloadditions.