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Moore Cyclizations: Rearrangements of 3-Heteroatom-pent-1-en-4-yn-1-ones – A Computational Search for New Reactions

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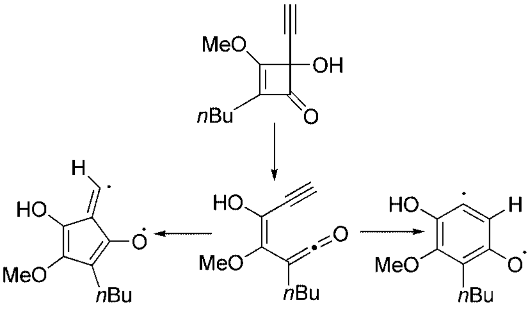
The thermal rearrangements of 3-heteroatom-pent-1-en-4-yn-1-ones were studied at the BLYP/6-311+G*//BLYP/6-31G* level of theory. While cyclizations to oxo-hetero-cyclopentadien-di-yl are most favorable and predicted to be experimentally feasible for X = CH^-, NH, O, and S, protonation of these substituents raises the corresponding 2,6-cyclization barriers. Cyclizations to oxacyclohexadienediyl are highly improbable due to competition with other low-lying alternative pathways.

Introduction

New chemical reactions are by and large discovered through serendipity and not–although some of us may naturally disagree–through systematic strategies. Computational methods can in principle be used to truly predict new reactions but this is rarely done in practice because it is dangerous to make bold predictions that can readily be tested. As we have demonstrated recently that one can indeed computationally predict new reactions *if* they come out of a *reaction family*[1,2] (i.e. they are very closely related) we apply this "heuristic approach" also to the cyclizations of enyne-ketenes in the present study.

(2-Alkynyl ethynyl) ketene (Scheme 1) generated in situ from the selective ring opening of 4-alkynylcyclobutenone[3] undergoes C^2–C^6 or C^2–C^7 cyclization to form five- and six-membered cyclic products, respectively.[4] Various substituents **R** have been probed experimentally to control the direction of the cyclizations; radical-stabilizing substituents **R**, such as alkoxy, phenyl, and trimethylsilyl, favor the 2,6-pathway and give five-membered rings. These reactions are assumed to involve diradical intermediates that are candidates for DNA cleavage.[5,6] Engels et al. computationally examined the biradical routes of these so-called Moore cyclizations of parent **1** (Scheme 2) to cyclic products **3** and **5**.[7] No study has been reported for the 1,7-reaction path (Scheme 2) leading to oxacycles **7** (oxepins), which are common in biologically active natural products.[8] Enyne-ketenes that are analogous to **2** with heteroatoms in place of the central olefinic bond have not been examined with respect to their cycloaromatization akin to **1** (Scheme 2). The present work reports on a systematic study of **2** as a building block for a new "reaction family"[1,2,9,10] and provides firm predictions regarding the formation of heterocycles through novel hetero-Moore reactions.



Scheme 1.

Previous studies on the rearrangements of heteroatom-substituted enyne-allenes[11] revealed the importance of **X** in donating its electron lone pair into the terminal methylene group; this effect overrides aromatic stabilization in the five-membered ring products. The σ-electron-withdrawing ability of **X** promotes the cyclizations by reducing the electron density from the electron-rich in-plane-π systems.[10, 11] For the current analysis of **2**, the choice of **X** is also crucial because the unfavorable 2 + 2 addition of the 2,6-cyclization requires **X** to be an σ-acceptor;[12] yet, the perpendicular π-system demands **X** to have an electron pair in conjugation with the molecular π-system to provide an aromatic sextet. With respect to **X**'s π-donating and σ-accepting abilities, various **X**s (Scheme 3) were considered. We systematically present the cyclizations of **2** to the *nonaromatic* oxo-hetero-cyclobutene derivative **4**, the formally *aromatic* oxo-

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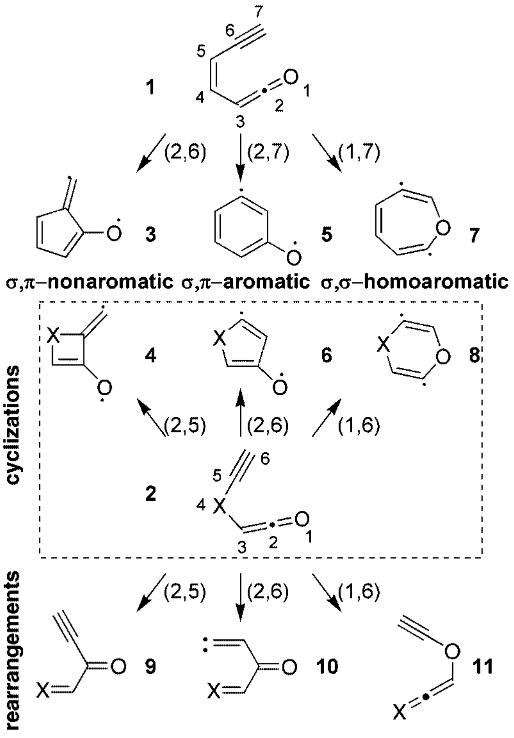
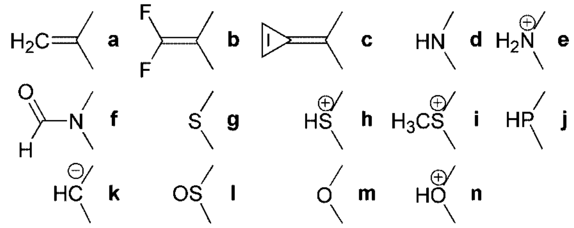


Scheme 2.

hetero-cyclopentadien-di-yl **6**, and the *homoaromatic* oxacyclohexadienediyl **8** (Scheme 2). Competing pathways such as the rearrangement of **2** to acyclic but-yn-ones **9**, to buten-ones **10**, and the formal hetero-Claisen reactions of **2** to en-ethynyloxy products **11** were also examined.



Scheme 3. Selection of **X** groups for the cyclization reactions of **2**.

Results and Discussion

In the reactions (through TS_{xy}) of **2** as a function of **X**, products **4**, **6**, and **8** are accompanied by competing rearrangements (through TS_{xy}') giving rise to acyclic products **9**, **10**, and **11** (Scheme 2); the prime indicates reaction paths leading to acyclic products. Existing reaction paths are coded by colors, i.e., dark, medium, and light gray colors, assigned to 2,5- (or 2,5′-), 2,6- (or 2,6′-), and 1,6- (or 1,6′-) reactions, respectively (Table 1). Energetics are only shown for the most favorable or competitive reactions. Table 2 provides relative energies at BLYP/6-311+G**//BLYP/6-31G* + ZPVE/6-31G* as well as the NICS[13] values for all cyclic species.

Table 1. Thermal rearrangements of **2** as a function of **X**: dark, medium, and light gray colors coded for the 2,5-, 2,6-, and 1,6-reaction, respectively; relative Gibbs activation ($\Delta G^{\ddagger}$, normal) and reaction free energies (ΔG, italics) at UBLYP/6-31G* shown only for energetically favorable or competitive pathways (in kcal mol^{-1}).

Products X	4	6	8	9	10	11
a	x[a]	34.8 *29.4*	n/a[b]	n/a[b]	n/a[b]	x[a]
b	x[a]	34.6 *26.9*	n/a[b]	n/a[b]	n/a[b]	x[a]
c	x[a]	31.9 *22.7*	n/a[b]	n/a[b]	n/a[b]	x[a]
d	x[a]	23.4 *6.9*	x[a]	n/a[b]	n/a[b]	n/a[b]
e	x[a]	30.4 *22.4*	n/a[b]	n/a[b]	n/a[b]	x[a]
f	x[a]	26.6 *12.3*	x[a]	n/a[b]	n/a[b]	n/a[b]
g	x[a]	32.2 *17.8*	n/a[b]	n/a[b]	n/a[b]	x[a]
h	n/a[b]	39.1 *33.4*	n/a[b]	38.1 *-12.5*	n/a[b]	36.3 *26.3*
i	n/a[b]	37.4 *32.1*	n/a[b]	36.2 *-10.7*	n/a[b]	36.6 *25.8*
j	n/a[b]	38.3 *33.6*	n/a[b]	x[a]	n/a[b]	x[a]
k	19.9 *14.1*	19.2 *-5.5*	x[a]	n/a[b]	n/a[b]	n/a[b]
l	n/a[b]	n/a[b]	n/a[b]	16.7 *-21.1*	x[a]	x[a]
m	x[a]	19.6 *2.6*	x[a]	n/a[b]	n/a[b]	n/a[b]
n	n/a[b]	x[a]	n/a[b]	23.4 *-54.1*	n/a[b]	10.5 *-3.4*

[a] Unlisted energetics for kinetically (barriers > 40 kcal mol^{-1}) or thermodynamically (endergonicities > 40 kcal mol^{-1}) highly unfavorable products. [b] Not accessible from the direct thermal rearrangements of **2**.

Although the experimental thermodynamics of the Moore cyclizations of parent **1** have not been determined,[6] Engels et al. reported computed Gibbs activation barriers for the C^2–C^6 and C^2–C^7 cyclizations of 41.4 and 13.6 kcal mol^{-1}, respectively, using the B3LYP/6-31G(d) level of theory. The corresponding reaction free energies are 24.8 and 4.8 kcal mol^{-1}; clearly, the C^2–C^7 ring closure is kinetically and thermodynamically favored. For the analogous 2,6-cyclizations of **2** (Scheme 2) our computed Gibbs activation barriers [BLYP/6-31G(d)] have a range of 19–39 kcal mol^{-1}, indicating the experimental feasibility (some at high temperatures only) of these heteroatom-substituted reactions (**X** = **k**, **m**, and **d**). Although the lowest barrier ($\mathbf{TS_{26}}$) of 19.2 for **X** = **k** is 5.6 kcal mol^{-1} higher than that of $\mathbf{TS_{27}}$ of parent **1**, the 2,6-reaction of **2** is thermodynamically favored as indicated by the computed exergonicity [$\Delta G(\mathbf{6}) = -5.5$ kcal mol^{-1}]. Note that the 2,6- and 2,7-cyclizations of the parent **1** are thermodynamically unfavorable.

For the reaction leading to cyclic products **4**, **6**, and **8**, the "aromatic" 2,6-reaction of **2** dominates over the nonaromatic 2,5- and homoaromatic 1,6-reactions both kin-

Table 2. Relative single point energies (kcal mol^{-1}), and NICS values (in the 4-, 5-, and 6-membered ring centers) at BLYP/6-311+G*//BLYP/6-31G* + ZPVE for the TSs and products of the thermal cyclization of 4-heteroatom-1,2-diene-5-ynes (**2**).

	BLYP/ 6-311+G*//BLYP/6-31G* + ZPVE					
X	$\Delta H_0^{\ddagger}$			NICS		
	TS_{25}	**TS_{26}**	**TS_{16}**	**TS_{25}**	**TS_{26}**	**TS_{16}**
a	53.5	37.8	63.3	74.3	–5.6	–20.8
b	51.6	37.4	67.3	17.0	–6.4	–21.9
c	44.9	33.9	61.0	30.5	–6.3	–20.4
d	38.1	25.2	36.6	6.2	–9.8	–17.6
e	53.9	32.5	30.9	–3.6	–5.5	–21.4
f	39.4	28.6	43.2	13.9	–8.3	–16.0
g	40.1	33.3	41.0	10.5	–9.9	–22.1
h	41.2	40.8	37.4	3.9	–6.8	–23.9
i	38.7	39.2	37.8	3.9	–6.7	–23.4
j	44.1	40.0	50.4	1.8	–9.3	–18.8
k	17.3	17.7	26.1	0.3	–9.0	–13.4
l	17.6	36.1	30.0	–8.8	–5.0	–17.9
m	32.1	21.9	37.8	14.4	–8.8	–19.1
n	26.6	29.2	11.9	2.2	–6.3	–14.1
	Products					
	ΔH_0			NICS		
	4	**6**	**8**	**4**	**6**	**8**
a	48.3	32.9	47.4	11.3	2.0	n/a[a]
b	47.1	30.9	52.3	7.3	0.1	n/a[a]
c	42.6	25.7	47.0	30.5	0.1	n/a[a]
d	36.1	10.0	37.5	5.9	4.1	–14.3
e	35.0	26.1	13.0	11.2	–3.1	n/a[a]
f	38.7	16.4	44.1	4.1	–3.4	–14.2
g	33.7	22.9	31.2	2.8	–5.2	n/a[a]
h	–11.6	36.3	27.7	n/a[a]	–3.8	n/a[a]
i	–9.6	34.9	27.7	n/a[a]	–3.7	n/a[a]
j	6.8	36.2	44.1	n/a[a]	–2.9	n/a[a]
k	12.4	–6.2	24.1	15.0	9.9	–6.6
l	–21.7	20.5	22.5	n/a[a]	n/a[a]	n/a[a]
m	26.0	6.6	39.4	6.2	–5.2	–15.9
n	–51.9	14.5	0.0	n/a[a]	–6.0	n/a[a]

[a] Unaccounted NICS values for products without ring formation due to either the C^3–X or C^5–X cleavages; this also indicates that their corresponding TSs lead to acyclic products **9**, **10**, and **11**, whose energies are listed in italics.

etically and thermodynamically; there are only a few exceptions. For **X** = **k**, the 2,5-reaction competes kinetically with the 2,6-reaction. With **X** = **h**, **i**, **l**, and **n**, the **TS_{25}′** barriers are lower than those of the 2,6-cyclizations (**TS_{26}**); the former reactions are also exergonic because stable acyclic ene-yne ketone products (**9**) result (Table 1).

High barriers for **X** = **f**, **m**, **d**, and **k** prevent the 1,6-cyclizations of **2**. Instead, **2** undergoes Claisen-type 1,6′-rearrangement cleaving the **C^3–X** bond to give acyclic **11**. Although for **X** = **e**, **h**, **i**, **l**, and **n** the Claisen-like reaction barriers (**TS_{16}′**) and the reaction energies [Δ*G*(**11**)] are energetically below those of the aromatic 2,6-reactions [Δ*G*(**TS_{26}**) and the Δ*G*(**6**)], this 1,6′-pathway competes with the 2,5′-reaction path forming the acyclic product **9** (vide infra).[14] Therefore, except for **X** = **e**, the 1,6′-reactions of **2** are highly improbable.

The dominance of the aromatic 2,6-cyclization path can be understood by analyzing its frontier molecular orbitals (FMOs). Figure 1 presents the FMOs study of **TS_{26}** with **X** = **CH^-** (= **k**) describing the transformation of the in-plane π-orbitals into the σ-orbitals (HOMO-2). Unlike the Myers–Saito reaction in which the methylene group rotates during the cyclization, the electronegative oxygen atom strongly polarizes the TS. The oxygen atom not only dispels the antibonding character of the σ-π-mixing MO across the C–C bond formation (HOMO-2) of the transition structure, but also withdraws the electron density across the π-MO perpendicular to the molecular plane (HOMO-1). While the former effect results in a significant reduction of the C^2–C^6 activation barrier of **2** (vide infra), the latter diminishes the aromatic-sextet stabilization expected in product **6**.

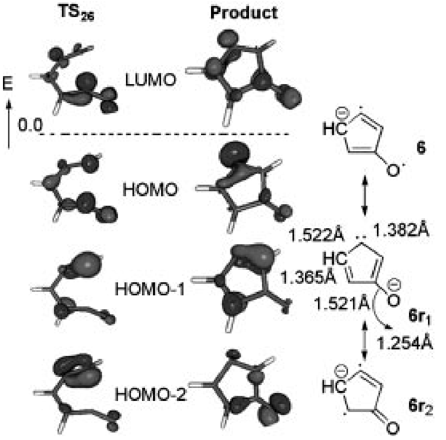


Figure 1. Frontier molecular orbital analysis of the transition structure and product of the 2,6-cyclization of **2** with **X** = CH^-.

Additionally, the bond lengths of C=O (1.254 Å) and C=X (1.365 Å, Figure 1) support the resonance forms of **6** (**6**↔**$6r_1$**↔**$6r_2$**, Figure 1). This can be seen in HOMO and HOMO-1 where the mixing is visible between the σ- and π-MOs. However, the notion of an aromatic sextet stabilizing the product, i.e., **X** providing a lone pair of electrons during the C^2–C^6 cyclization, is not corroborated by the computed thermodynamic stabilization. The contribution of the **X** lone pair can be turned off by protonation, i.e., **X** = **d**, **g**, and **m** vs. **e**, **h**, and **n**. As a consequence, the Gibbs activation barriers of the protonated forms [Δ*G*(**TS_{26}**)] are uniformly higher by about 7.0 kcal mol^{-1} (Table 1), resulting from the inability to form an aromatic electron sextet or stable resonance forms.

Conclusions

We conclude that out of the very many reactions possible for the cyclizations or rearrangements of starting heteroatom ketene-alkyne **2**, only very few are chemically relevant: with some rare exceptions, *aromatization* reactions to hetero-substituted furans **6** are preferred, irrespective of the heteroatom and the charge state. Hence, this "*heuristic chemistry*" approach to identify new chemical reactions by means of systematic computational comparisons of available reactions pathways helps to predict novel transformations that now await experimental verification. As many of the starting materials of type **2** can be readily prepared (e.g., X = **k** or **m**), this is a realistic goal.

Computational Methods

Becke's pure gradient-corrected exchange functional[15] in conjunction with the Lee–Yang–Parr non-local correlation functional (BLYP)[16] and the 6-31G* basis set were utilized for all optimizations, as implemented in Gaussian03.[17] Open-shell singlet state transition structures (TSs) and products computed with a broken-spin approach (UBS-BLYP), while all closed-shell species were computed with the restricted method. Thermal corrections and zero-point vibrational energies (ZPVE) were determined by evaluating analytical second derivatives to characterize minima and transition structures. Additional single-point energies with the same functional but with a larger basis set (6-311+G*) were also computed for all species. UBS-DFT has been a practical tool to provide good qualitative results for cyclizations of polyunsaturated systems.[1,18,19] Elaborate multireference calculations are currently too time-consuming for the large number of structures considered in the present study. Single-point Brueckner Doubles computations [BD(T)][19,20] with a cc-pVDZ basis set using the DFT geometries were computed for comparison in critical cases.

Supporting Information (for details see the footnote on the first page of this article): *x*,*y*,*z* coordinates, structural drawings, and a table of energies (including <S2> values) of all computed species.

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