Rules for Anionic and Radical Ring Closure of Alkynes

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S *Supporting Information*

ABSTRACT: This work reexamined the stereoelectronic basis for the "favored attack trajectories" regarding the nucleophilic and radical cyclizations of alkynes. In contrast to the original Baldwin rules, the acute attack angle of a nucleophile leading to the proposed endo-dig preference for the formation of small cycles is less favorable stereoelectronically than the alternative obtuse trajectory leading to the formation of exo-dig products. For smaller cycles, this intrinsic stereoelectronic preference can be masked by the greater thermodynamic stability of the less strained endo-products. Unbiased comparison of competing cyclization attacks has been accomplished via dissection of the activation barrier into the intrinsic barrier and thermodynamic component via Marcus theory. Intrinsic barriers of thermoneutral reactions strongly favor exo-dig closures, in full accord with the greater magnitude of two-electron bond forming interactions for the obtuse trajectory. This analysis agrees very well with experimental observations of efficient 3-exo-dig and 4-exo-dig cyclizations predicted to be unfavorable by the Baldwin rules and with the calculated 3-exo-/4-endo-, 4-exo-/5-endo-, and 5-exo-/6-endo-dig selectivities in the cyclizations of carbon-, nitrogen-, and oxygen-centered nucleophiles. The generality of these predictions is confirmed by analogous trends for the related radical cyclizations where the stereoelectronically favorable exo-closures are also preferred kinetically, with a few exceptions where a large difference in product stability skews the intrinsic stereoelectronic trends.

INTRODUCTION

Since up to 90% of organic molecules in nature contain either a carbocyclic or a heterocyclic subunit,[1] it is not surprising that the 1976 paper on "Rules for Ring Closure" by Sir Jack E. Baldwin became the most cited article in the >40-year history of RSC Chemical Communications (Figure 1).[2] Not only did this work define the nomenclature and the vocabulary for describing and classifying ring closure steps, but it also combined the existing empirical knowledge with basic stereoelectronic considerations to predict the favorable modes of cyclization.[3]
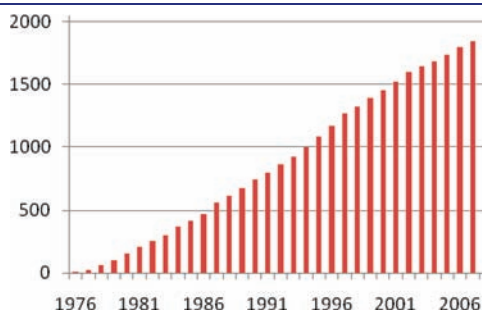

Figure 1. Citations of the "Rules for Ring Closure" (1976−2010).

The classification system is based on three independent variables: the number of atoms in the new ring, hybridization of the attacked atom and whether the breaking bond is outside (exo) or inside (endo) of the forming cycle (Scheme 1). Favored ring closures are expected "when the length and nature of linking chain enables the terminal atoms to achieve the required trajectories"[3] for the final ring bond formation (Scheme 2). In contrast, disfavored reactions require severe distortion in order to reach the optimal trajectories.

In defining the favorable ring closure trajectories at the carbon atom, Baldwin suggested that: "In each case (tetragonal, trigonal, digonal) the subtended angle α between the three interacting atoms is maintained during the reaction pathway, becoming the angle between these atoms in the product." In addition to the least motion considerations, two of the proposed trajectories also had a clearly defined stereoelectronic component: the "tet" trajectory followed the 180° attack angle for an S_N2 reaction, whereas the ∼105−109° angle on sp^2 atoms corresponds to the Bürgi-Dunitz[4] angle for nucleophilic attack at a carbonyl. These trajectories optimize the overlap of incoming nucleophiles with the acceptor σ^*_{C-Y} (tet) and $\pi^*_{C=Y}$ (trig) orbitals (Scheme 3).

Apart from a few exceptions,[5] the Baldwin rules have been very successful for tet- and trig-cyclizations. However, the situation is different for the dig-cyclizations. We outline our reasons for revisiting the cyclizations of alkynes below.

Contrasting Rules for Trig and Dig Cyclizations. Because of the very limited experimental evidence available at the time,[6,7] Baldwin chose the acute angle of attack β (60°, Scheme 3c)

Scheme 1. Baldwin's Classification for the Cyclizations forming 3-, 4-, and 5-Membered Cycles[a]
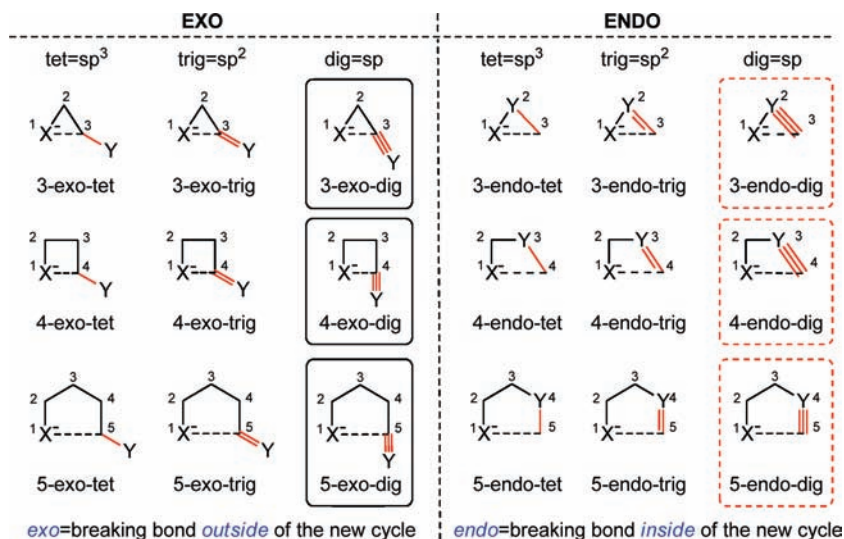
[a] Breaking bonds are shown in red, forming bonds are shown in dashed lines; tet (tetragonal) = sp³, trig (trigonal) = sp², dig (digonal) = sp. Reactions reexamined in this work are boxed. Black boxes, exo-dig cyclizations; red dashed boxes, endo-dig cyclizations.

Scheme 2. (Top) Baldwin's Predictions for the Formation of 3-, 4- and 5-Membered Cycles;[a] (Bottom) Suggested Modification for the Digonal Cyclizations[b]


[a] Favorable cyclizations (labeled "√") are in green boxes, unfavorable cyclizations (labeled "×") are in red boxes. 3-Endo-tet and 4-endo-tet were not included in the original rules but are generally considered to be unfavorable (labeled "a" in grey boxes). [b] Note the 5-endo-dig cyclization is only favorable when certain conditions are met (vide infra). See Table 4 for a more detailed set of rules which further differentiate nucleophilic and radical closures.

rather than an obtuse angle (120°, Scheme 3d) as the preferred trajectory for the intramolecular nucleophilic attack at the triple bond. This trajectory choice led to the prediction that endo-closures are favored in digonal cyclizations of alkynes, in stark contrast with the exo-preference in analogous cyclizations of alkenes (Scheme 4). The suggested preference for the endo attack in digonal cyclizations also contrasted the suggested general preference for radical exo-cyclizations suggested by Beckwith.[8]

Contrary to the above model summarized in Scheme 4, the mounting body of experimental and theoretical evidence,

Scheme 3. (a–c) The Original Trajectories Suggested by Baldwin for Tetrahedral (a), Trigonal (b), and Digonal (c) Cyclizations; (d) the Alternative Obtuse Trajectory[a]
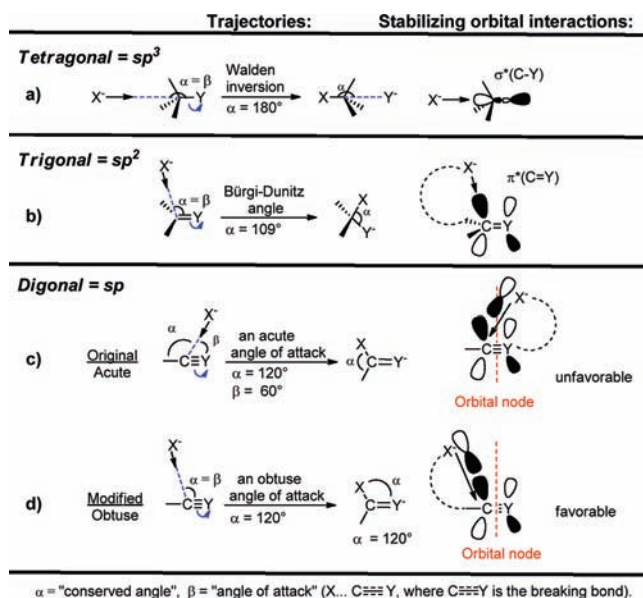
[a] Note that the "conserved angle α" is different from the attack angle β for the acute trajectory in alkynes. Dominant bond-forming interactions are shown on the right.

including the results presented in the following sections of this work, suggests that the acute trajectory is stereoelectronically unfavorable (as shown in Scheme 3c). As this trajectory brings the nucleophile at the node of the target π*-orbital, this mismatch in orbital symmetry should decrease the magnitude of the 2-electron stabilizing interactions and disfavor the new bond formation. In contrast, the obtuse trajectory (analogous to the stereoelectronically favorable Bürgi-Dunitz trajectory

Scheme 4. "Ideal" Trajectories and Contrasting Predictions for Trig- and Dig-Cyclizations in the Original Baldwin Rules
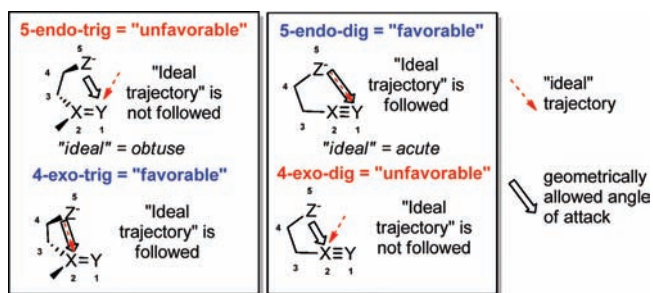
for -trig cyclizations) does not suffer from the unfavorable orbital interactions.

The discrepancy between the proposed acute trajectory and basic stereoelectronic considerations is further illustrated by the reported similarity for the intermolecular attack angles at the C≡C and the C=C moieties.[9,10] Recent calculations at higher levels of theory[11] including our data provided in the Supporting Information further support the notion that the attack trajectories and TS geometries follow a Bürgi-Dunitz-like obtuse trajectory for nucleophilic addition to alkynes and alkenes. Our trajectories of intermolecular attack by three model nucleophiles (CH$_3^-$ (114.0°), NH$_2^-$ (122.5°), OH$^-$ (129.1°), M05-2X/6-31G(d,p) level (see Supporting Information)) on the triple bond of ethyne fully agree with the earlier computations and the intrinsic stereoelectronic preference for the obtuse attack.

If the above intermolecular attack trajectories and stereoelectronic preferences are transferrable to their intramolecular counterparts, the obtuse approach should provide a better trajectory for nucleophilic cyclizations of alkynes. *In this situation, the original predictions of favorable endo-dig cyclizations and unfavorable exo-dig cyclizations should be reversed.* This paper aims to test whether such predictions based on attack trajectories are valid.

The predictive power of an analysis based solely on stereoelectronic factors is compromised, however, by the fact that for many reactants, thermodynamic factors favor the formation of a *larger* cycle, that is, the *endo*-closure. The thermodynamic contribution can strongly impact the activation barrier,[12,13] potentially overriding the intrinsic stereoelectronic preferences in those cases where the smaller cycle is considerably more strained. This is particularly relevant for alkynes because attack at the in-plane π-system partially alleviates the distortion strain observed in achieving the Bürgi-Dunitz angle for the endo-cyclizations of alkenes where the attack at the out-plane π-system is the only option.[14]

We will start with the computational analysis of nucleophilic digonal closures. We will then investigate whether cyclizations follow the preferred angles of intermolecular attack on alkynes using carbon-, nitrogen-, and oxygen-centered anionic nucleophiles. In the discussion of stereoelectronic factors in competition cyclizations, we will use energy dissection based on the Marcus theory. This dissection will allow us to provide an unbiased comparison of cyclization paths without the complications arising from different thermodynamic contributions to the activation barrier.

Because anionic closures can be influenced by the nature of counterions, solvent, and the oligomeric nature of carbanionic species, we will expand this treatment to the analogous radical cyclizations, where such side effects are of a lesser importance.[15]

We will conclude with a critical discussion of experimental data which has become available after the introduction of the original Baldwin rules. We will conclude the manuscript with a new set of guidelines for the nucleophilic and radical cyclizations of alkynes and a brief outline of factors important for other cyclization types (electrophilic and mixed types, vide infra).

■ COMPUTATIONAL DETAILS AND METHODS

Reactant, TS, and product geometries for the cyclizations were optimized using the Gaussian 03 program.[16] All of the geometries were characterized to be minima with no imaginary frequencies except for transition state geometries that were shown to be first order saddle-points with a single imaginary frequency. All transition state energies are given relative to the energy minimum closest to the near attack conformation. The computational data are given at the B3LYP and M05-2X levels of theory with the 6-31+G** basis set. B3LYP is one of the most commonly used "workhorses" of computational chemistry, whereas M05-2X is reported to give more accurate thermochemistry for organic systems.[17] The performance of nine other DFT methods, as well as high level CCSD(T) calculations, has been tested as well (see the Supporting Information).

The direct effect of thermodynamic factors on activation barriers can be estimated with Marcus theory.[18−20] This approach dissects the energy of activation ($\Delta E^{\ddagger}$) into the intrinsic barrier and the thermodynamic contribution. The intrinsic barrier ($\Delta E_o^{\ddagger}$) represents the barrier of a thermoneutral process ($\Delta E_{rxn} = 0$). The thermodynamic contribution can either be positive or negative depending on whether the reaction is endothermic or exothermic. The activation energy increases when $\Delta E_{rxn} > 0$ (an endothermic reaction) and decreases when $\Delta E_{rxn} < 0$ (an exothermic reaction). When the potential energy surfaces for the reactants and the products are approximated as parabolas, the Marcus barriers can be calculated from eq 1.[21]

$$\Delta E^{\ddagger} = \Delta E_o^{\ddagger} + \frac{1}{2}\Delta E_{rxn} + (E_{rxn})^2/16(\Delta E_o^{\ddagger}) \qquad (1)$$

Alternatively, when the energy of activation ($\Delta E^{\ddagger}$) and reaction energy (ΔE_{rxn}) are known, one can estimate the intrinsic barrier ($\Delta E_o^{\ddagger}$) from the modified Marcus eq 2.[14] Because ΔE_o is the barrier for a reaction free of any thermodynamic bias, eq 2 allows one to compare intrinsic stereoelectronic preferences for cyclizations of different exothermicity.

$$\Delta E_o^{\ddagger} = \frac{\Delta E^{\ddagger} - \frac{1}{2}\Delta E_R + \sqrt{\Delta E^{\ddagger 2} - \Delta E^{\ddagger}\Delta E_R}}{2} \qquad (2)$$

NICS computations were done at the B3LYP/6-311+G** level on B3LYP/6-31+G* geometries using the GIAO procedure which provides the isotropic shift of NMR parameters.[22]

■ RESULTS AND DISCUSSION

Computational Analysis of Anionic Dig-Cyclizations. We have scanned the performance of several DFT methods for the set of parent anionic cyclizations. The results presented below (Table 1) provide the first computational analysis of basic nucleophilic cyclization types performed in a systematic way.

Activation Barriers. In contrast to the Baldwin rules, the calculations find that *barriers for all exo-dig closures of carbanions are lower than for the respective endo-dig cyclizations.* The >20 kcal/mol difference between 3-exo and 4-endo closures is particularly striking because the parent 4-endo-dig cyclization is about

Table 1. Activation, Reaction, and Intrinsic Energies (kcal/mol) for the Parent Anionic Cyclizations at the B3LYP/6-31+G(d,p) and M05-2X/6-31+G(d,p) Levels of Theory; M05-2X Data Are Given in Parentheses

Reaction schemes: 3-exo/4-endo ⇒; 4-exo/5-endo ⇒; 5-exo/6-endo. X=CH₂, NH, O; R= H, Me, Ph, TMS

3-exo-dig/4-endo-dig

Reactant	Product	E_a	ΔE_r	ΔE_o	Reactant	Product	E_a	ΔE_r	ΔE_o
CH₂	(structure)	7.75 (9.24)	-5.44 (-7.47)	10.29 (12.70)	CH₂	(structure)	7.79 (8.96)	-4.48 (-7.37)	9.90 (12.37)
	(structure)	29.53 (32.30)	-11.75 (-14.02)	35.16 (38.99)		(structure)	27.03 (29.39)	-12.99 (-16.13)	33.21 (37.02)
NH	(structure)	13.62 (12.55)	10.38 (6.01)	7.53 (9.30)	CH₂ ...Ph	(structure)	7.32 (6.24)	-7.74 (-13.49)	10.84 (12.04)
	(structure)	38.69 (39.10)	6.62 (1.31)	35.30 (38.44)		(structure)	32.37 (32.07)	-12.07 (-19.02)	38.17 (41.03)
O	(structure)	$-^a$	-	NA	CH₂ ...TMS	(structure)	7.53 (6.47)	-3.34 (-7.57)	9.12 (9.89)
	(structure)	46.45 (46.08)	21.88 (19.02)	34.65 (35.94)		(structure)	30.11 (30.91)	-4.03 (-8.45)	32.09 (35.01)

4-exo-dig/5-endo-dig

Reactant[b]	Product	E_a	ΔE_r	ΔE_o	Reactant	Product	E_a	ΔE_r	ΔE_o
CH₂	(structure)	7.32 (8.95)	-14.39 (-16.79)	13.56 (16.26)	CH₂	(structure)	7.67 (8.93)	-11.92 (-15.21)	12.94 (15.61)
	(structure)	8.45 (10.35)	-34.04 (-39.06)	22.21 (26.25)		(structure)	8.10 (9.39)	-33.62 (-39.75)	21.65 (25.37)
NH	(structure)	12.74 (14.39)	1.29 (-0.79)	12.09 (14.78)	CH₂ ...Ph	(structure)	3.83 (3.84)	-21.97 (-28.36)	12.38 (14.56)
	(structure)	11.96 (13.59)	-15.01 (-19.78)	18.71 (22.39)		(structure)	7.29 (6.69)	-37.01 (-47.34)	21.88 (24.69)
O	(structure)	18.17 (19.42)	16.04 (14.38)	8.19 (11.06)	CH₂ ...TMS	(structure)	4.39 (4.36)	-14.70 (-18.76)	10.45 (11.89)
	(structure)	16.69 (17.81)	1.67 (-3.27)	15.84 (19.41)		(structure)	6.28 (6.24)	-27.69 (-35.39)	17.37 (20.03)

5-exo-dig/6-endo-dig

Reactant[b]	Product	E_a	ΔE_r	ΔE_o	Reactant	Product	E_a	ΔE_r	ΔE_o
CH₂	(structure)	1.31 (3.32)	-35.91 (-40.61)	13.12 (22.86)	CH₂	(structure)	1.32 (2.32)	-32.50 (-39.07)	12.13 (15.82)
	(structure)	10.71 (11.08)	-38.97 (-43.81)	17.85 (28.82)		(structure)	8.53 (7.82)	-37.81 (-45.09)	23.66 (25.35)

Table 1. Continued

5-exo-dig/6-endo-dig

Reactant[b]	Product	E_a	ΔE_r	ΔE_o	Reactant	Product	E_a	ΔE_r	ΔE_o
NH (alkyne)		8.82 (10.67)	-13.44 (-17.19)	*14.78 (18.25)*	CH₂···Ph	Ph	.[c]	-45.64 (-54.25)	*NA*
	HN	18.40 (18.30)	-13.94 (-19.06)	*24.88 (26.99)*		Ph	9.19 (10.92)	-41.65 (-52.13)	*25.82 (31.61)*
O⁻ (alkyne)		11.80 (13.39)	5.80 (1.90)	*8.66 (12.42)*	CH₂···TMS	TMS	1.06 (1.54)	-33.61 (-40.97)	*11.96 (15.06)*
	O	18.98 (19.59)	4.27 (-0.50)	*16.78 (19.84)*		TMS	8.02 (4.40)	-30.05 (-39.30)	*20.26 (18.96)*

[a] The ring-opening reaction is barrierless. [b] Energies are given relative to the near-attack conformations (NAC). The anti-anti conformation is ~4–5 kcal/mol more stable than the NACs (see the Supporting Information). [c] This cyclization is barrierless. See section on thermodynamic contribution to the reaction barrier and the Supporting Information for further discussion.

~7 kcal/mol <u>more</u> exothermic than its 3-exo-dig counterpart but the 3-exo closure still has a much lower barrier!

Interestingly, the calculated exo-endo difference decreases to ~1 kcal/mol for the 4-exo/5-endo pair but increases again to >9 kcal/mol for the 5-exo/6-endo pair.[23] An analogous situation is observed for the N- and O-anions where the computations suggest a clear exo-preference for the 3-exo-/4-endo-dig and for 5-exo-/6-endo-dig pairs but a much closer competition for the 4-exo-/5-endo-dig closures. In fact, the endo-barriers are predicted to be 1–2 kcal/mol lower for these heteroatomic nucleophiles.

We suggest that this seemingly irregular trend does not stem purely from the stereoelectronic factors, but rather originates from their interplay with thermodynamic contributions to the activation barrier (vide infra). When thermodynamic driving forces for the two cyclizations are similar (<u>both</u> products are either strained (3-exo/4-endo) or not (5-exo/6-endo)), there is a clear kinetic preference for the exo-path. Only for the special case where the exo-product is much more strained than the endo-product (the 4-exo/5-endo pair) and the endo-cyclization is much more exothermic, the exo/endo kinetic competition becomes relatively close.[24] Considering the above, let us examine the reaction thermodynamics closer.

Thermodynamics of Digonal Nucleophilic Ring Closure. Even for the formation of strained cycles, all *carb*anionic cyclizations are exothermic and effectively irreversible due to the conversion of a weaker bond into a stronger bond (π-bond → σ-bond) and the concomitant transformation of an alkyl anion into a more stable vinyl anion. This is true even for the formation of strained 3-exo and 4-endo products. In contrast, the analogous cyclizations of the parent N- and O-centered anions transform a *hetero*atom-centered anion into a *carb*anion. The energy cost due to this unfavorable change is substantial. For the N-anions, this effect renders 3-exo cyclization ~10 kcal/mol endothermic whereas the 4-endo and 4-exo closures are essentially thermoneutral. Note that, for these cyclizations, B3LYP significantly underestimates reaction exothermicity in comparison to M05-2X but the activation energies provided by the two methods and the higher level CCSD(T) calculations are similar (see the

Supporting Information). For the O-anions, all reactions leading to the formation of 3- and 4-membered rings are strongly endothermic, whereas formation of 5- and 6-membered rings is either thermoneutral or weakly endothermic. Such unfavorable cyclizations should be quickly reversible—for example, ring-opening of the 3-exo product has only ~3 kcal/mol activation barrier for the N-case whereas the analogous opening to the more stable O-centered anion is barrierless *in silico*.

Computational Analysis of Radical Dig-Cyclizations. To test the generality of this analysis, we have expanded this study to the analogous radical cyclizations (Table 2). Radical cyclizations play an important role in benchmarking computational methods because these reactions are less sensitive to the many external factors which affect anionic closures (nature of counterion, solvent, etc.).

Interestingly, although the large kinetic exo-preference remains evident, the relative thermodynamic driving forces of radical and anionic cyclizations are quite different.[25] These differences stem from electronegativity effects displayed in two different ways. First, digonal cyclizations of nitrogen- and oxygen-centered radicals do not suffer from the same penalty as cyclizations of the respective anions (conversion of a stable heteroatom-centered anion into a carbanion). As the result, the cyclization energy profiles for carbon- and heteroatom-centered radicals are not as different as they were for the respective anions. Second, unlike vinyl anions, vinyl radicals do not have greater stability relative to their alkyl analogues. As the result, although all carbanionic cyclizations are more favorable thermodynamically than their radical counterparts, the situation is just the opposite for the oxygen-centered species where the radical cyclizations are more exothermic (Figure 2). Nitrogen occupies an intermediate position.

The radical 3-exo-, 4-endo- and, possibly, 4-exo-dig cyclizations of carbon radicals are endothermic and, thus, are unlikely to be practically viable in their simplest versions as presented in Table 2. These data are consistent with the absence of 3-exo and 4-endo-dig radical cyclizations in the literature. Instead, the cyclic products of such exo-cyclizations are expected to undergo a fast ring opening similar to the ring opening of cyclopropylmethyl

Table 2. Activation, Reaction, and Intrinsic Energies (kcal/mol) for the Parent Radical Digonal Cyclizations at the B3LYP/6-31+G(d,p) and M05-2X/6-31+G(d,p) Levels of Theory; M05-2X Data Are Given in Parentheses

Reaction scheme: 3-exo/4-endo ⇒ 4-exo/5-endo ⇒ 5-exo/6-endo. X = CH$_2$, NH, O; R = H, Me, Ph, TMS

3-exo-dig/4-endo-dig

Reactant	Product	E_a	ΔE_r	ΔE_o	Reactant	Product	E_a	ΔE_r	ΔE_o
˙CH$_2$	(cyclopropyl)	16.26 (17.32)	8.16 (7.20)	11.83 (13.48)	˙CH$_2$ (R=Me)	(cyclopropyl)	16.58 (17.66)	8.20 (7.14)	12.31 (13.86)
	(cyclobutyl)	36.43 (38.32)	5.37 (4.34)	33.69 (36.12)		(cyclobutyl)	34.39 (36.12)	6.13 (4.67)	31.25 (33.74)
˙NH	HN (cyclopropyl)	18.31 (19.68)	12.01 (10.90)	11.52 (13.69)	˙CH$_2$ (R=Ph)	Ph (cyclopropyl)	12.43 (13.39)	2.43 (1.70)	11.18 (12.53)
	HN (cyclobutyl)	34.20 (36.85)	10.82 (10.54)	28.53 (31.36)		Ph (cyclobutyl)	34.96 (35.73)	5.38 (3.10)	32.21 (34.16)
˙O	O (cyclopropyl)	15.17 (16.94)	8.78 (7.73)	10.31 (12.78)	˙CH$_2$ (R=TMS)	TMS (cyclopropyl)	15.41 (16.04)	8.61 (7.71)	10.67 (11.87)
	O (cyclobutyl)	32.31 (35.39)	13.29 (12.05)	25.23 (29.05)		TMS (cyclobutyl)	37.60 (38.63)	13.80 (11.63)	30.31 (32.56)

4-exo-dig/5-endo-dig[a]

Reactant	Product	E_a	ΔE_r	ΔE_o	Reactant	Product	E_a	ΔE_r	ΔE_o
˙CH$_2$	(cyclobutyl)	18.02 (19.11)	0.44 (0.27)	17.80 (18.97)	˙CH$_2$ (R=Me)	(cyclobutyl)	17.82 (19.06)	0.41 (0.09)	17.61 (19.01)
	(cyclopentyl)	17.95 (18.44)	-16.44 (-18.90)	25.51 (27.07)		(cyclopentyl)	17.95 (18.00)	-14.05 (-17.34)	24.47 (25.95)
˙NH	N–H (cyclobutyl)	20.88 (23.25)	2.09 (1.57)	19.82 (22.46)	˙CH$_2$ (R=Ph)	Ph (cyclobutyl)	14.96 (15.65)	-5.61 (-5.92)	17.65 (18.49)
	HN (cyclopentyl)	21.37 (23.16)	-11.02 (-13.50)	26.59 (29.52)		Ph (cyclopentyl)	18.85 (17.94)	-13.69 (-18.62)	25.23 (26.43)
˙O	O (cyclobutyl)	17.89 (21.54)	-0.12 (-0.85)	17.95 (21.96)	˙CH$_2$ (R=TMS)	TMS (cyclobutyl)	17.38 (18.24)	0.84 (0.73)	16.96 (17.87)
	O (cyclopentyl)	20.69 (23.82)	-10.18 (-13.26)	25.53 (30.08)		TMS (cyclopentyl)	19.63 (18.64)	-6.60 (-11.01)	22.81 (23.83)

5-exo-dig/6-endo-dig[a]

Reactant	Product	E_a	ΔE_r	ΔE_o	Reactant	Product	E_a	ΔE_r	ΔE_o
˙CH$_2$	(cyclopentyl)	7.29 (7.49)	-20.56 (-22.91)	15.91 (17.02)	˙CH$_2$ (R=Me)	(cyclopentyl)	7.10 (7.39)	-20.41 (23.10)	14.67 (16.98)
	(cyclohexyl)	9.91 (10.22)	-27.08 (-29.75)	21.30 (22.65)		(cyclohexyl)	10.35 (9.93)	-23.79 (-27.69)	20.52 (21.55)

Table 2. Continued

5-exo-dig/6-endo-dig[a]

Reactant	Product	E_a	ΔE_r	ΔE_o	Reactant	Product	E_a	ΔE_r	ΔE_o
		10.08 (11.81)	-17.83 (-20.25)	*17.88 (20.70)*			4.45 (4.72)	-26.52 (-28.77)	*14.72 (16.09)*
		11.24 (13.05)	-21.1 (-24.16)	*20.43 (23.58)*			11.88 (10.85)	-22.51 (-27.93)	*21.67 (22.66)*
		7.19 (10.17)	-18.52 (-21.69)	*15.0 (19.51)*			6.74 (6.69)	-19.72 (-21.95)	*14.98 (15.75)*
		7.20 (9.69)	-21.04 (-24.82)	*15.99 (20.19)*			12.00 (10.66)	-16.29 (-21.28)	*19.28 (19.88)*

[a] The anti-anti conformation is more stable than the starting material (see the Supporting Information).

radicals, commonly referred to as "radical clock".[26] However, the significant decrease in endothermicity for the cyclization of the Ph-substituted alkyne suggests that, with a proper effort, it may be possible to shift the equilibrium in favor of the cyclic form and to design efficient 3-exo-dig radical cyclizations, as has been accomplished for the respective trigonal closures.[27]

In a sharp contrast with the respective anionic cyclizations, 4-exo radical cyclization of the parent radical is essentially thermoneutral ($\Delta E_r \sim 0$), whereas the 5-endo-closure is still significantly exothermic. Remarkably, the calculated activation barriers suggest that the 4-exo-dig closure should be capable of competing kinetically with the much more exothermic 5-endo-dig closure. For the parent carbon-centered radical, the 4-exo and 5-endo barriers are very close.[28]

The exothermicity of radical reactions increases as the ring size increases. In contrast, the exothermicity of the 5-exo and 6-endo closures for both N- and O-centered anions is slightly lower than the respective 5-endo-dig closure.

Thermodynamical Component to the Activation Energies: Unmasking Intrinsic Barriers and Stereoelectronic Preferences. Even under kinetic control, thermodynamic contributions can modify selectivity and relax intrinsic stereoelectronic preferences in two ways. First, in accord with the Hammond-Leffler postulate,[29] exothermic reactions have early, reactant-like transition states and consequently require less distortion from the reactant geometry in order to reach the TS.[30] Decreased distortions often alleviate geometric requirements needed to reach the optimal bond-forming trajectories.

Second, thermodynamic contributions directly lower the activation barriers in exothermic reactions relative to the barriers of the analogous thermoneutral or endothermic processes. As a result, it is inappropriate to take the observed activation barriers as a measure of intrinsic stereoelectronic preferences when the compared reactions have drastically different exothermicities. To have an unbiased comparison, the compared reactions should have equal thermodynamic driving forces.

Figure 3 illustrates this notion and shows how an intrinsically unfavorable reaction (cyclization #2) becomes fast once it has been made sufficiently exothermic. As the result, even under kinetic control, the observed reaction selectivity can indirectly reflect the differences in reaction thermodynamics.

To eliminate the effect of different thermodynamic contributions on the activation energies of anionic dig-cyclizations, we determined the intrinsic activation energies for these processes using Marcus theory as outlined above in the description of theoretical methods (ΔE_o, eq 2). Since the intrinsic barriers are free from thermodynamic bias, they allow comparison of inherent stereoelectronic factors and favorabilities for related processes with different thermodynamic driving forces.

The ΔE_o values reveal that, for all digonal cyclizations reported above, *exo-closures are always stereoelectronically preferred over the endo-closures*, independent of the linker and the nature of the nucleophile (Figure 4). *The endo-dig cyclizations are only able to compete with the exo-closures in those cases (e.g., the 4-exo/5-endo pair) where thermodynamic contribution overcomes the intrinsic stereoelectronic preferences.*[31]

The same dissection for the radical ring closures reveals that the key trends are analogous to those observed for the anionic closures: *independent of the linker and the nature of attacking radical, exo-closure is intrinsically preferred to the endo-radical attack* (Figure 5). Very interestingly, the exo- preference starts to erode for the larger cycle formation from the more electrophilic (N- and O-centered) radicals (vide infra).

It is also interesting to compare the intrinsic barrier trends for anions and radicals. For exo-cyclizations, the intrinsic barriers are slightly lower for the respective anionic cyclizations (especially for N- and O-centered species). However, for 4-endo- and 6-endo-dig cyclizations, the situation is just the opposite: intrinsic endo-barriers are lower for the radical closures than for the analogous anionic closures.[32] The greater preference for exo-attack in anions than in radicals is due to the change in the nature of dominant bond forming interactions for the two types of species ($n \to \pi^*$ in anions vs $n \to \pi^* + \pi \to n$ in radicals).

One has to bear in mind that the energy dissection in eq 1 approximates reactant and product energy profiles as having identical simplified curvatures, and, thus, can describe reactions with nonsymmetric energy profiles only approximately. To gain further insight into the scope and accuracy of this
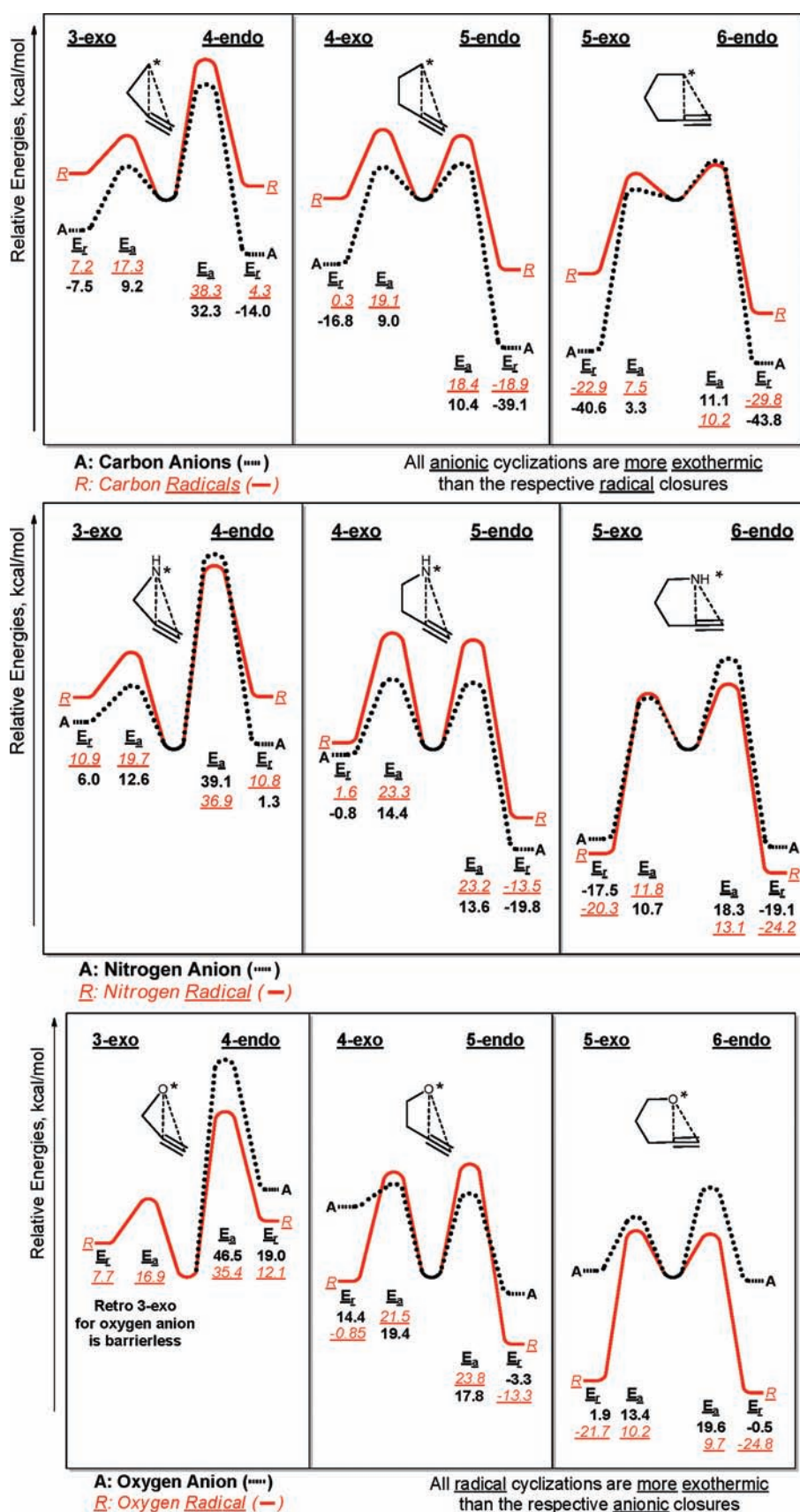
Figure 2. Electronegativity effects on the M05-2X/6-31+G** potential energy surfaces for the anionic and radical cyclizations of the parent C-, N-, and O-centered anions (black dashed, bold) and radicals (red solid, italics, underlined) with terminal alkynes.
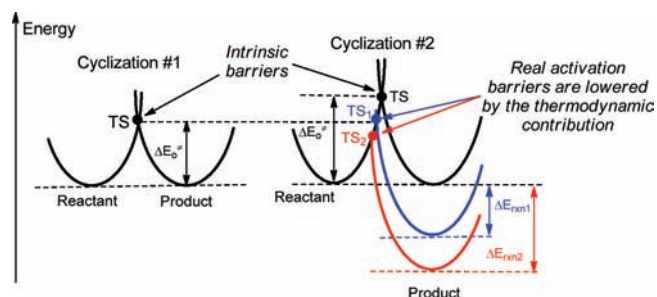
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Figure 3. Thermodynamic effects on the activation energy and use of Marcus theory for approximating potential energy curves and separating intrinsic barriers from thermodynamic contributions. In the absence of thermodynamic bias, the intrinsically unfavorable cyclization #2 has a higher barrier. The parabolic model illustrates how the activation barrier for the unfavorable cyclization becomes identical (blue curve, TS_1) to the barrier for the favorable reaction #1. Upon a further increase in thermodynamic driving force for reaction #2 (red curve, TS_2), this cyclization becomes faster than the initially favored process #1.
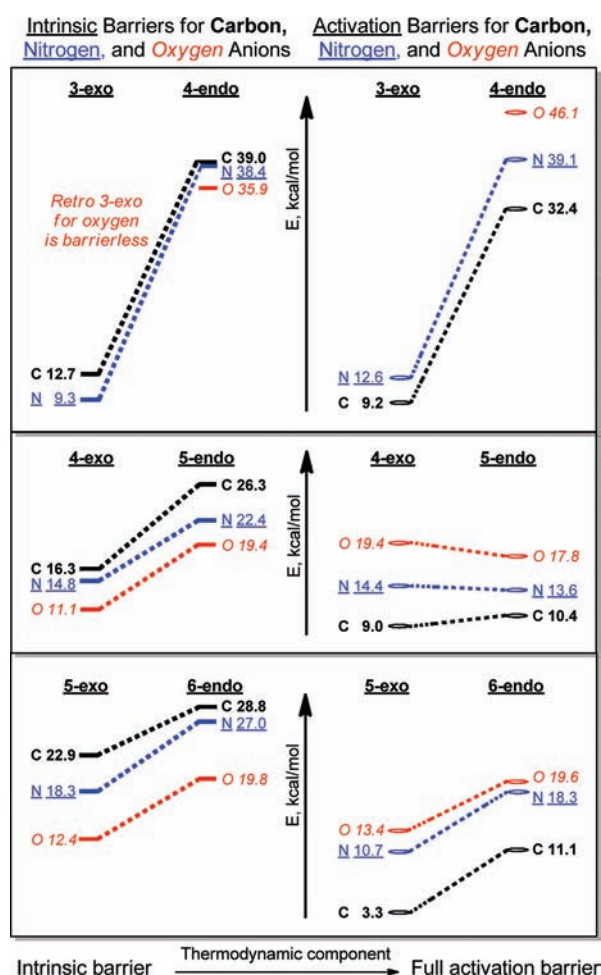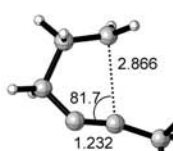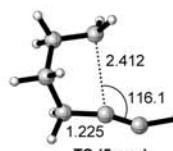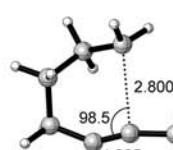

Figure 4. Intrinsic (left) and activation (right) barriers for the cyclizations of carbon- (black, bold), nitrogen- (blue, underlined), and oxygen- (red, italics) anions with terminal alkynes at M05-2X/6-31+G(d,p) level of theory. Note how intrinsic 4-exo/5-endo selectivity is masked by thermodynamic effects.

analysis, we have expanded it to a set of substituted acetylenes, comparing anionic and radical cyclizations in parallel. These
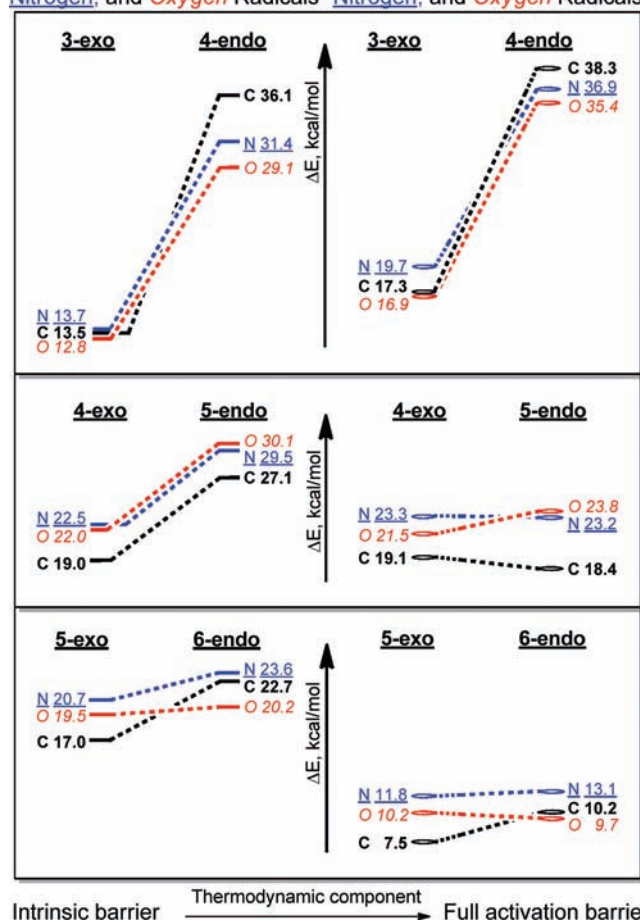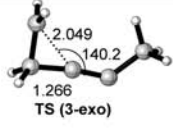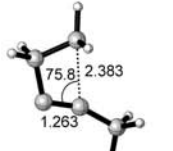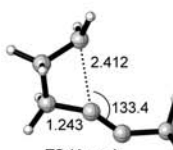
Figure 5. Intrinsic (left) and activation (right) barriers for the cyclizations of carbon- (black, bold), nitrogen- (blue, underlined), and oxygen- (red, italics) radicals with terminal alkynes at M05-2X/6-31+G(d,p) level of theory. Note the distortion of intrinsic 4-exo/5-endo selectivity by thermodynamic effects and erosion of exo-selectivity for the 5-exo/6-endo cyclizations of heteroatom-centered radicals.

comparisons are presented in the Supporting Information. The intrinsic barriers vary slightly depending on the nature of substituents, suggesting that substituent effects are, to some extent, already in play at the transition state and that the contribution of substituents is not limited solely to the effect on reaction exothermicity. However, the variations are relatively minor, indicating that the underlying stereoelectronic factors for each of the cyclizations are only moderately perturbed by the alkyne substitution. Moreover, Marcus approximation readily explains the disappearance of activation barrier for R = Ph (see the Supporting Information).

Transition State Geometries and Stereoelectronics of Nucleophilic Cyclizations. Comparison of intrinsic energies in the previous sections clearly shows that, in every case, independent of the nature of nucleophile and alkyne substitution, exo-cyclizations have lower intrinsic barriers than their endo-competitors. In this section, we will analyze the geometries of the cyclization transition states and key stereoelectronic factors involved in the bond-forming interactions of the nucleophile lone pair (n_{Nu}) with the alkyne π^* orbital.

Table 3. Transition State Geometries and Intrinsic Activation Barriers for 3-Exo/4-Endo, 4-Exo/5-Endo, and 5-Exo/6-Endo Carbanionic Cyclizations for the Me-Substituted Alkyne Calculated at the M05-2X/6-31+G** Level[a]

TS Geometry	ΔE_0
2.049 / 140.2 / 1.266 — TS (3-exo)	9.9 (12.4)
75.8 / 2.383 / 1.263 — TS (4-endo)	33.2 (37.0)
2.412 / 133.4 / 1.243 — TS (4-exo)	12.9 (16.3)
2.866 / 81.7 / 1.232 — TS (5-endo)	21.7 (25.4)
2.412 / 116.1 / 1.225 — TS (5-exo)	12.1 (15.8)
2.800 / 98.5 / 1.225 — TS (6-endo)	23.7 (25.4)

[a] Bond lengths given in Å, energies in kcal/mol.

The calculated TS geometries in Table 3 illustrate the effect of cyclic restraints on attack trajectories. As the linker length increases, the obtuse angle of the exo-attack decreases from 140° (3-exo) to 116° (5-exo), approaching the angle for the intermolecular attack (vide supra). At the same time, the incipient C···C distance increases, indicating earlier transition states for the more exothermic cyclizations (3-exo < 4-exo < 5-exo). Interestingly, the intrinsic exo-barriers change relatively little (12.4−16.2 kcal/mol), indicating that such variations in the attack trajectory are well tolerated.
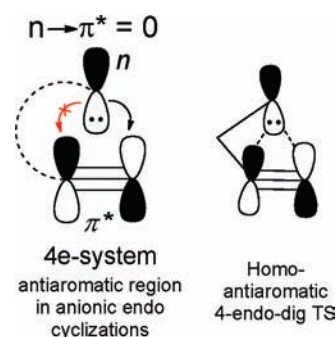

Figure 6. "Antiaromatic regions" in anionic endo-cyclizations.

For the endo-attack in small cycles, the cyclic constraints impose an acute angle of nucleophilic attack (76° for 4-endo- and 82° for 5-endo-closures). As the cycle size increases, the angle of attack changes to a more favorable obtuse approach in 6-endo-dig closure. As expected, 4-endo- and 5-endo-cyclizations have much earlier transition states than the less exothermic competing exo-closures. Only in the 5-exo/6-endo pair is the Hammond-Leffler postulate violated and a more exothermic reaction has a slightly later transition state. All intrinsic endo-barriers are relatively high (25−37 kcal/mol), especially for the 4-endo-dig closure.

The remarkably high transition state energy (~30 kcal/mol) for the endothermic[33] 4-endo-dig cyclizations of the parent but-3-ynyl carbanion results from a symmetry mismatch in the key bond forming interaction between the anionic center and the in-plane alkyne π^*-orbital, which cancels out the stabilizing two-electron $n(C) \rightarrow \pi^*$ interaction and endows this orbital interaction pattern with homoantiaromatic character (Figure 6).[34−36]

Survey of Experimental Data. The combination of DFT computations and stereoelectronic models presented in the previous sections suggests that anionic and radical exo-dig cyclizations should be feasible. The experimental data, discussed below, further supports this notion.

Overall, the situation has changed dramatically over the years since the inception of the original Baldwin rules. Only a handful of experimental examples of digonal cyclizations were available at the time when the rules were created. In particular, Baldwin cited the work of Kandil and Dessey,[37] who compared the reactivities of carbanions generated in close proximity to acetylenic groups at different geometries. In the first case, neither 3-exo nor 4-endo closure has been observed (Figure 7a). In the second case, the anionic species closed in a 5-endo-dig fashion (Figure 7b). In the final example, the aryl anion cyclized expediently and exclusively in a 5-exo-dig fashion (Figure 7c).

At that time, the above "parallel" example was the only meaningful experimental evidence for an acute attack leading to the endo product in a digonal cyclization. However, the observed lack of obtuse attack forming the 4-exo-product is likely to be an artifact of additional strain imposed by the polycyclic core, which constrains reacting functionalities in a parallel geometry, significantly distorting the intrinsic selectivity. Moreover, the observed lack of 6-endo cyclization products in the less strained "convergent array" is inconsistent with the suggested preference for the acute trajectory (Figure 7c). Although one cannot exclude the assistance of the terminal aryl group in the formation of an exocyclic product via increased stabilization to the incipient anionic center, it is clear that the experimental data
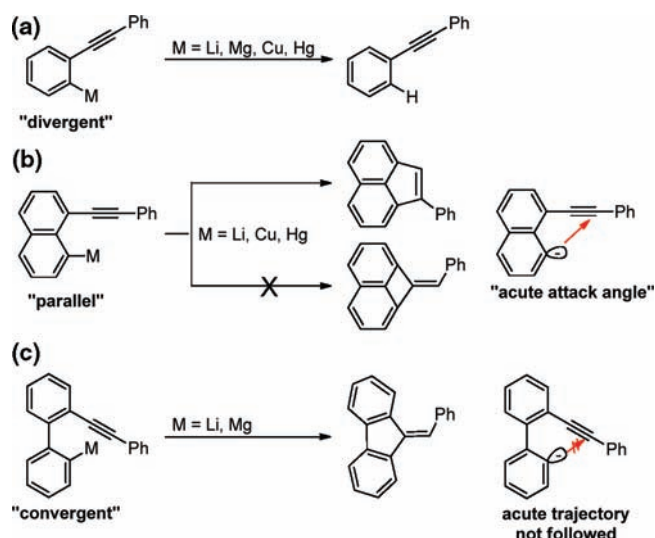
Figure 7. Three examples used to define the original Baldwin rules for alkynes. (a) With a divergent angle of 60°, only the reduced product is obtained; (b) a "neutral" parallel array with the angle of 0° results in 5-endo-dig closure of the carbanion; (c) a convergent angle of 60° exclusively yields the 5-exo-dig product. The expected acute attack angle is shown with a red arrow.
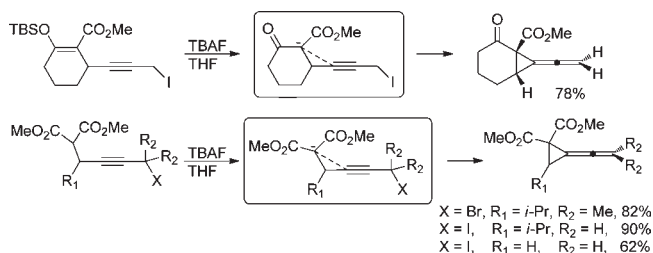
Scheme 5. Carbanionic 3-Exo-Dig Cyclization

Scheme 6. Representative Nucleophilic 4-Exo-Dig Cyclizations

Scheme 7. Effect of alkyne polarization on the regioselectivity of anionic closure

available in 1976 was limited. We will show below that information from recent decades provides a firmer ground for establishing reliable guidelines for digonal cyclizations.

3-Exo/4-Endo. The prediction of 3-exo-dig anionic cyclizations to be a favorable process is consistent with the exclusive formation of 3-exo-products in the only unambiguous experimental example of a truly nucleophilic cyclization of a homopropargylic nucleophile reported thus far.[38] Because this reaction found by Johnson and co-workers involves stabilized enolates as reactants, it is thermodynamically feasible only when coupled with an irreversible elimination of a propargylic halide (Scheme 5).[39]

Even considering that the above cyclization is coupled with an elimination step, which may provide additional assistance to the exoclosure, the report of an "unfavorable" 3-exo-dig cyclization of nucleophilic species being fast under ambient conditions is especially significant because both anionic and radical 4-endo-digonal closures (favorable according to the original Baldwin rules) remain, to the best of our knowledge, unknown.[28,40] Our computational results suggest that this situation is unlikely to change. Even though the 4-endo-dig closures are predicted to be significantly exothermic, the extremely high 4-endo-dig barriers suggest that both this cyclization mode and the ring opening of 4-endo products are kinetically unfavorable.

In contrast, according to our computational results, the 3-exo-dig closures of nonstabilized anions should be possible even without special efforts, such as trapping of the product via an irreversible elimination step. *Remarkably, such cyclizations are still unknown but, in this case, the search should continue!* The same applies to the so far unknown 3-exo-dig *radical* cyclizations. Although these, relatively fast, cyclizations are endothermic and should be reversible, it may be possible to accomplish them via coupling to another, thermodynamically favorable step (e.g., fragmentation or subsequent exothermic cyclization).[28] Such strategies have been successful for other endothermic radical processes, such as O-neophyl rearrangement in a recently
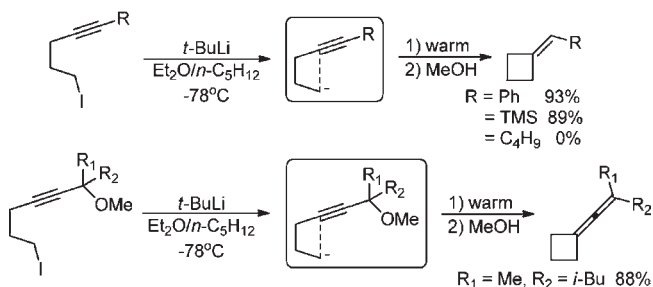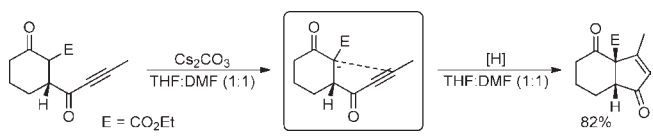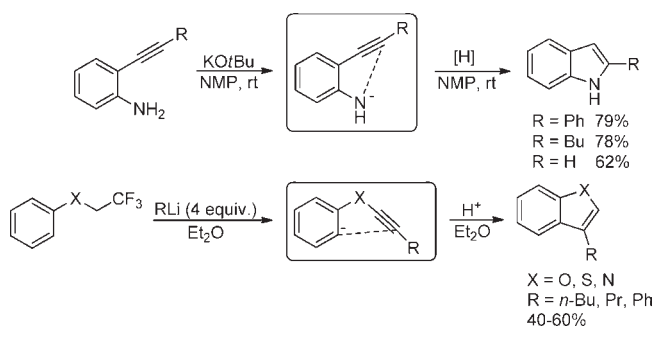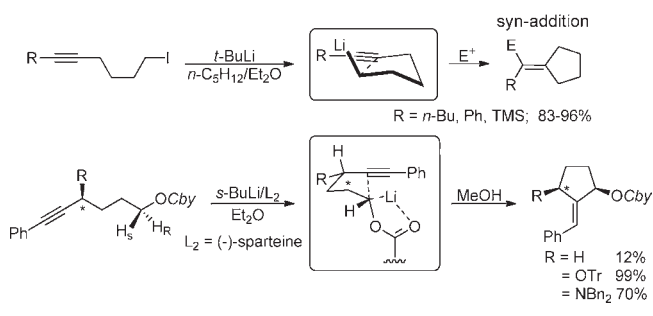
reported metal-free transformation of phenols into benzoates and benzamides.[41]

4-Exo/5-Endo. The computed difference between 4-exo and 5-endo anionic closures in the parent and Me-substituted alkynes is relatively small (>1.2 kcal/mol). Although these two cyclizations should be quite fast (E_a 7−10 kcal/mol) for the "naked" carbanions, neither cyclization is known experimentally for nonactivated alkynes. Similar to the above 3-exo-closures, such 4-exo-cyclizations have been only successful in the presence of an appropriate leaving group at the propargylic position.[42] The "unfavorable" 4-exo-dig closures have been reported by Bailey and Ovaska to be "unexpectedly rapid and clean" for R = Ph and TMS (Scheme 6).[43,44] 4-Exo closure is also facilitated by such terminal substituents as bulky boranes[45] and esters[46] capable of stabilizing the exocyclic anionic center.

Although these experimental results clearly show that the "unfavorable" 3-exo- and 4-exo-dig closures are preferred to the "favorable" 4-endo-dig and 5-endo-dig closure in cyclizations of simple nucleophiles,[47] the computed kinetic exo-preference is not as large for the 4-exo/5-endo pair as it is for the 3-exo/4-endo pair. In accord with this small difference, stereoelectronics can be overridden and efficient 5-endo-dig cyclizations can be designed via several approaches. For example, the regioselectivity of nucleophilic attack can be

**Scheme 8. 5-Endo-Dig Closures Leading to the Formation of Aromatic Products**

R = Ph 79%
R = Bu 78%
R = H 62%

X = O, S, N
R = n-Bu, Pr, Ph
40-60%

Scheme 9. Selected sp³-Anionic 5-Exo-Dig Closures with Completely Saturated Linkers

syn-addition

R = n-Bu, Ph, TMS; 83-96%

L₂ = (-)-sparteine

R = H 12%
= OTr 99%
= NBn₂ 70%

Scheme 10. Base-Catalyzed 5-Exo-Dig Cyclizations of Primary and Secondary Alcohols onto Terminal Triple Bonds[a]

ref 66a

R = H, 0%
R = Me, 80% ref 65

anti-addition

99% ref 68

Carbanion is antiperiplanar
to the acceptor σ*C-O orbital

[a] Benzylic alcohols also close regioselectively onto phenyl-substituted acetylenes.

Scheme 11. The Solvent-Dependent Switch between Kinetic and Thermodynamic Control in the Digonal Cyclization of Oxygen Anions

A = Acetone 8% : 85%
B = EtOH 79% : 15%

reversed by polarizing the triple bond with a carbonyl group at the interior propargylic position. This effect leads to a clean (82%) 5-endo-dig cyclization of an enolate, even though the carbanionic orbital in the cyclic product is constrained perpendicular to the π-bond of the carbonyl moiety (Scheme 7).[48]

Formation of 5-endo-dig products in anionic cyclizations of N-nucleophiles can also be assisted by aromaticity of the products.[49] An alternative pathway to yield aromatic products is also possible, which includes the cyclization of an aryl carbanion onto a heteroatom-substituted alkyne (40–60%, Scheme 8).[50]

A similar situation has been observed for the radical 4-exo and 5-endo-dig pairs where 4-exo-dig closure was found to be kinetically preferred.[51,52] The preference, however, is not absolute and, in the presence of kinetic and/or thermodynamic factors facilitating the 5-endo closure, the selectivity can be shifted in favor of the latter process,[29,53] as illustrated by a recent discovery of the first efficient C—C formation via a 5-endo-dig radical cyclization.[29]

5-Exo/6-Endo. Cyclizations of alkyl lithium reagents, generated from alkyl iodides and connected to an alkyne via a fully saturated linker, proceed exclusively via the 5-exo-dig pathway.[54] Bailey and co-workers have analyzed this process comprehensively and found no evidence for 6-endo-dig product formation.[61b] Although the cyclization is sluggish for R = Bu, the phenyl- and TMS-substituted analogues react expediently.[55,56] Stereoselective syn-addition suggests a concerted intramolecular Li transfer to the developing carbanionic center (Scheme 9). As this metal coordination cannot be preserved en route to the 6-endo-dig TS, it is possible that this factor
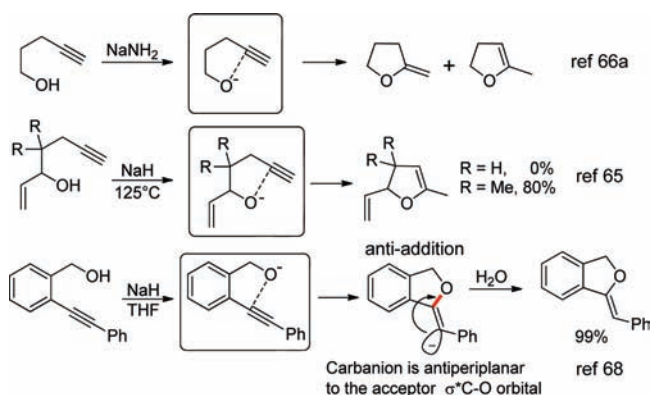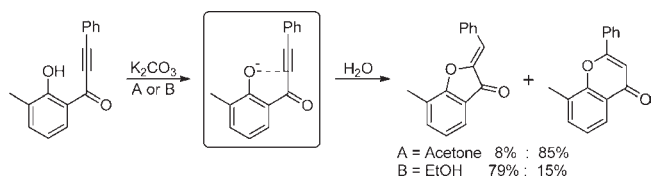
contributes to the observed 5-exo preference as well. Myers and co-workers have utilized the regioselective 5-exo closure of a vinyl anion in the development of synthetic approaches toward Kedarcidin and related natural products.[57]

Base-catalyzed cyclizations of aliphatic or benzylic alcohols exclusively follow the 5-exo pathway (Scheme 10).[58–60] Interestingly, 5-exo-dig cyclization of simple oxygen nucleophiles is anti-stereoselective.[61] We suggest that this effect is due to hyperconjugative stabilization of the anion with antiperiplanar σ^*(C—O)-orbital.[62]

Even strong alkyne bond polarization is not always sufficient for overriding the intrinsic exo-preference. For example, Miranda and co-workers[63] found that the "anti-Michael" exo-dig product is formed in 79% yield in a protic solvent (EtOH) (Scheme 11) where the kinetically favorable 5-exo cyclized carbanion is quickly trapped by protonation. In an aprotic solvent (acetone), the initially formed 5-exo-dig vinyl anion has enough time to rearrange to the more stable 6-endo-dig product, as has been suggested in similar systems by Padwa and co-workers.[68] Tietze and co-workers have used this strategy for six-membered ring formation in their syntheses of anthrapyran antibiotics.[64] Although 5-exo-preference is observed for the cyclization of nitrogen nucleophiles as well, the regio- and stereoselectivities are sensitive to nature of substituents at the nitrogen.[65]

The question of 5-exo/6-endo selectivity in radical cyclizations of alkynes has been thoroughly investigated. Although the general preference is for the formation of 5-exo-products,[66,67] the 6-endo-dig cyclization becomes competitive in fully

conjugated systems where the 6-endo-products are aromatic and in systems where the 5-exo products are disfavored by strain.[68]

Rules for Digonal Cyclizations. The summary of computational and experimental data summarized above suggests that, even though experimental gaps still exist, the formation of small cycles via anionic and radical exo-dig cyclizations is stereoelectronically favorable and the search for these reactions should continue.

Although the continuing progress of science leads to the systematic redesign of (and occasional departure from) existing paradigms, rendering each new set of "rules" a potentially risky proposition, several trends of potentially broad and lasting importance do emerge from this study. First, "favorability" has several possible definitions: intrinsic stereoelectronics which originate from the differences in the orbital overlap patterns, and full activation barriers which combine the intrinsic barriers with thermodynamic components. From the fundamental and didactical perspectives, the first definition is valuable but the second is more useful in practice. On the basis of the first criterion, one can clearly classify all exo-dig cyclizations as favorable, 4-endo-dig as unfavorable, and 5-endo dig as a borderline case (Table 4.). However, thermodynamic factors impose their effect on these intrinsic preferences in two ways. First, they increase the activation barriers rendering both 3-exo and 4-exo closures less kinetically favorable

Table 4. Revised Baldwin Rules for of Anionic and Radical Digonal Cyclizations[a]

Anionic		3	4	5	6
Dig	endo-	x [(b)]	x	✓	✓
	exo-	✓	✓	✓✓	✓✓ [(b)]

Radical		3	4	5	6
Dig	endo-	x [(b)]	x	✓	✓✓
	exo-	✓	✓	✓✓	✓✓ [(b)]

[a] Red squares (×) correspond to disfavored, yellow squares (✓) to borderline/problematic, and green (✓✓) to favored modes of ring-closure. [b] These cyclizations were not analyzed in the present work and predictions are based solely on basic stereoelectronic factors extrapolated from computational results for the other cyclizations.

than these reactions would be with a normal thermodynamic driving force. Second, anionic 5-endo-dig cyclizations of less reactive nucleophiles are exothermic, whereas the competing 4-endo-dig closures are not. As the result, the 5-endo-dig closures should be feasible and even favorable under these circumstances.

Another intriguing consequence of this analysis is that the stereoelectronic guidelines should change depending on the type of reactive intermediates, as the very nature of the bond-forming interactions defining the favorable trajectories changes as well. The effect of the reacting species begins to manifest itself in the noticeably greater favorability of radical 6-endo cyclizations[69] in comparison to their anionic counterparts.

The differences between anionic and cationic cyclizations should be much larger. For example, unlike nucleophilic attack at the alkyne π^*-orbital (LUMO), the 2e bond-forming interaction in an electrophilic attack involves the alkyne π-orbital (HOMO). Not only is there no node in the π-orbital in the direction of the approaching electrophile, but stabilizing orbital interactions directly lead to the formation of nonclassical 3c–2e complexes, well-documented for cationic attack. As a result, *there should not be any stereoelectronic penalty for the acute trajectory for electrophilic approach and cationic endo-cyclizations*. Although a *thermodynamic* penalty for the formation of endo-cyclic vinyl cation[70] (due to incorporation of a sp-hybridized carbon in a cycle) *does* exist for electrophilic closures, it can be decreased if nucleophilic attack occurs simultaneously, intercepting the cation and assisting the ring closure.[71]

Yet another conceptually different approach for modifying the regioselectivity of *nucleophilic* closures includes changing the alkyne LUMO symmetry via coordination with a suitable Lewis acid (I^+, Ag^+, I_2, etc.). Although the new LUMO is antibonding <u>between</u> the Lewis acid and the alkyne, its symmetry for the <u>backside</u> nucleophile approach in a ring closure step is identical to that of a π-orbital (e.g., the HOMO of the free alkyne). As a result, such Electrophile-Promoted Nucleophilic Closures (EPNC) offer no stereoelectronic penalty for the endo-approach of a nucleophile to the target π-system as well (Figure 8).
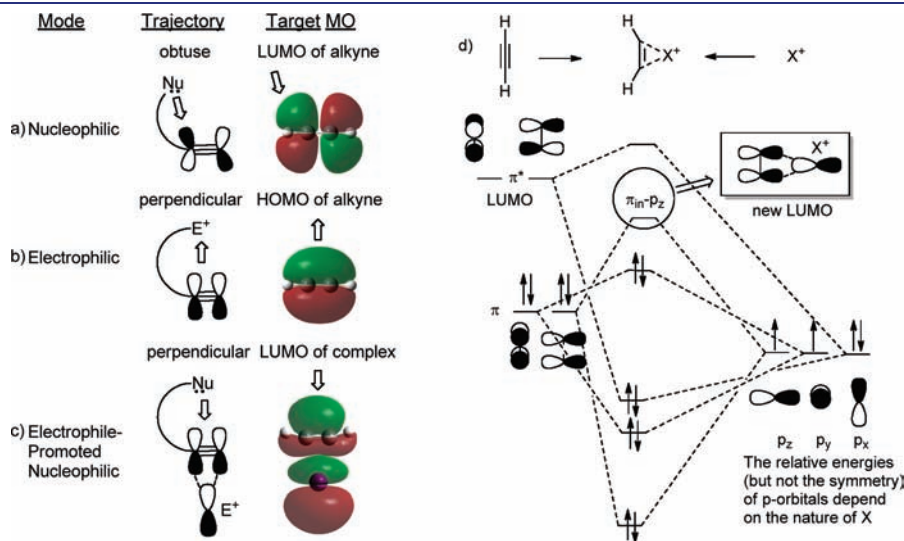

Figure 8. Summary of the key stereoelectronic factors involved in bond forming interactions during different modes of ring formation from alkynes. (a and b) The FMOs of C_2H_2. (c) The LUMO of the I^+-acetylene complex. Note the analogous symmetry of the top part of the LUMO of the complex and the acetylene HOMO. (d) MO mixing diagram which shows how the alkyne LUMO symmetry changes upon coordination.

The two approaches outlined in the previous paragraphs illustrate how stereoelectronic limitations of nucleophilic ring closures can be overridden, enabling the design of selective endo-dig cyclizations. We will report our quantitative analysis of such processes in the near future.

■ SUMMARY

In this general overview of the basic patterns of anionic and radical cyclizations, we have restricted our discussion to the most fundamental trends in structure and reactivity.[72] Many other features of these reactions, such as effect of substitution on intrinsic energies, role of hyperconjugation on stereoselectivity, and role of solvents, additives, and counterions in the aggregation state of anionic acyclic species, deserve more careful analysis which we hope to provide in our future work. However, the combination of computational, theoretical, and experimental data presented herein clearly shows that both anionic and radical endo-dig cyclizations are intrinsically less favorable than the competing exo-dig closures. The origin of this preference lies in the greater magnitude of stabilizing bond-forming interactions for the obtuse angle of nucleophilic (and to a lesser extent, radical) attack. This stereoelectronic preference is similar to the well-established Bürgi-Dunitz trajectory for the cyclizations of alkenes. Intrinsic stereoelectronic preferences for exo-dig closure can be overshadowed by additional factors, such as polarization of the π-system and thermodynamic effects (e.g., strain in one of the products and/or aromaticity in the other), which can tip the balance in favor of the endo-products. In our future work, we will expand our analysis to the cationic dig-cyclizations and more unusual processes such as nucleophile-promoted electrophilic and electrophile-promoted nucleophilic closures of alkynes.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Calculated activation and reaction energies at different DFT levels in comparison with CCSD-(T) data; relative energies for different conformations of starting materials; Cartesian coordinates of all geometries (including their total energy) which involve in this study. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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■ ACKNOWLEDGMENT

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(31) Interestingly, intrinsic barriers for carbanionic cyclizations are higher in every case than intrinsic barriers for the heteroatomic nucleophiles. This difference may be due to either the steric hindrance imposed by substituents at carbon or the presence of additional lone pairs at the anionic heteroatom centers, or a combination thereof.

(32) The 5-endo-dig closure looks special: the intrinsic barrier for anionic cyclization is lower than what one would expect based on extrapolation using the rest of the data. We will discuss this effect in following sections.

(33) Even for the endothermic 4-endo-dig closures of the parent N- and O-anions, the 4-endo products reside in a very deep potential energy minima which provide ~25 kcal/mol of barrier protection even for the oxetene anion. The anomalously high barriers for the four-membered ring openings suggest, according to the macroscopic reversibility principle, that the transition states for the endo-dig anionic ring closures suffer from strong electronic destabilization. Again, this notion is in strong contradiction with the original Baldwin guidelines and suggested preference for an acute trajectory for the nucleophilic attack at the triple bond.

(34) A corollary of this analysis is that cationic endo-closures should not carry the same stereoelectronic penalty as the nucleophilic cyclizations. This prediction will be tested in our subsequent work.

(35) Homoantiaromaticity is consistent with the positive value (+3.1) for the NICS(0) in the center of the forming 4-membered ring. NICS(0) rather than NICS(1) has been used because the antiaromatic system includes *the in-plane π- and p-orbitals*. This value may underestimate antiaromaticity because NICS(0) has significant contribution from other σ-orbitals. NICS(0) for the 3-exo-TS is strongly negative. For recent discussions of homoaromaticity, see: (a) Holder, A. *J. Comput. Chem.* **1993**, *14*, 251. (b) Williams, R. V. *Chem. Rev.* **2001**, *101*, 1185. (c) Stahl, F.; Schleyer, P. v. R.; Jiao, H.; Schaefer, H. F., III; Chen, K.-H.; Allinger, N. L. *J. Org. Chem.* **2002**, *67*, 6599. Homoaromaticity in transition states: (d) Jian, H.; Nagelkerke, R.; Kurtz, H. A.; Williams, V.; Borden, W. T.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1997**, *119*, 5921. Homoaromaticity in carbenes and cationic intermediates: (e) Freeman, P. K.; Dacres, J. E. *J. Org. Chem.* **2003**, *68*, 1386. Bishomoaromatic Semibullvalenes: (f) Goren, A. C.; Hrovat, D. A.; Seefelder, M.; Quast, H.; Borden, W. T. *J. Am. Chem. Soc.* **2002**, *124*, 3469. Homoaromatic and antiromatic hyperconjugative patterns: (g) Alabugin, I. V.; Manoharan, M.; Zeidan, T. A. *J. Am. Chem. Soc.* **2003**, *125*, 14014.

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