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Iodine

Mapping the Interactions of I_2, $I^{\bullet}$, I^-, and I^+ with Alkynes and Their Roles in Iodocyclizations

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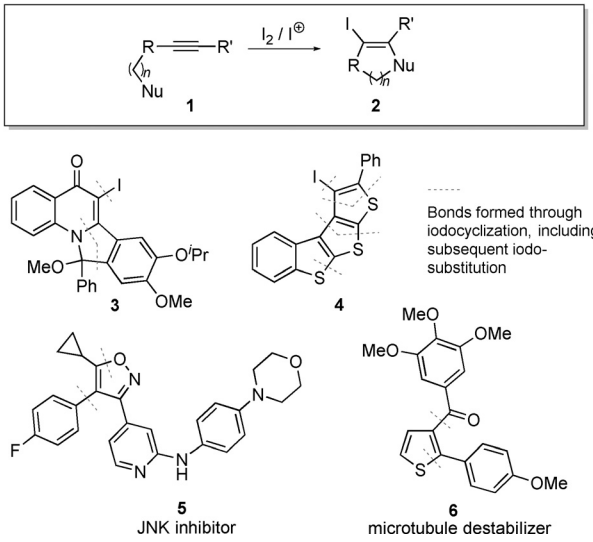
Abstract: A combination of experiment and theory has been used to explore the mechanisms by which molecular iodine (I_2) and iodonium ions (I^+) activate alkynes towards iodocyclization. Also included in the analysis are the roles of atomic iodine ($I^{\bullet}$) and iodide ion (I^-) in mediating the competing addition of I_2 to the alkyne. These studies show that I_2 forms a bridged I_2–alkyne complex, in which both alkyne carbons are activated towards nucleophilic attack, even for quite polarized alkynes. By contrast, I^+ gives unsymmetrical, open iodovinyl cations, in which only one carbon is activated toward nucleophilic attack, especially for polarized alkynes. Addition of I_2 to alkynes competes with iodocyclization, but is reversible. This fact, together with the capacity of I_2 to activate both alkyne carbons towards nucleophilic attack, makes I_2 the reagent of choice (superior to iodonium reagents) for iodocyclizations of resistant substrates. The differences in the nature of the activated intermediate formed with I_2 versus I^+ can also be exploited to accomplish reagent-controlled 5-*exo*/6-*endo*-divergent iodocyclizations.

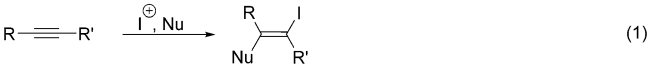
Introduction

Electrophilic activation of π bonds by halides and halonium ions is an area of great significance to organic synthesis.[1] Over the last 15 years, the iodocyclization of alkynes bearing tethered nucleophiles (Scheme 1, **1**→**2**) has emerged as one of the most important synthetic applications of electrophilic π-activation.[2,3] Iodocyclizations provide access to an enormous variety of carbo- and heterocyclic structures (**2**: R and Nu = carbon and/or heteroatoms, n = 1–3) including benzofurans, indoles, benzothiophenes, quinolones, isoquinolines, imidazoles, isoxazoles, thiophenes, furans, pyrroles, pyranones, lactones, and heptenones (see Scheme 1 for examples).[2,3] Iodocyclization chemistry also enables the construction of more complex polycyclic systems, for example by iodine or iodonium ion-induced reaction cascades (e.g., **3**) or reiterative alkyne coupling/iodocyclization strategies (e.g., **4**).[4,5] The versatility and scope of this chemistry are evidenced by the rapid uptake into drug discovery (e.g., **5** and **6**) and materials design efforts.[5–7]



Scheme 1. Iodocyclization of alkynes and applications in chemical synthesis.

Apart from mediating iodocyclizations, electrophilic activation of alkynes by iodonium reagents has been used to provide convenient stereo- and regioselective access to tri- and tetrasubstituted alkenes [Eq (1)].[8] Moreover, the elimination of I_2 from *trans*-diiodoalkenes has recently been employed to convert polydiiododiacetylenes into conducting graphenes [Eq (2)].[9]



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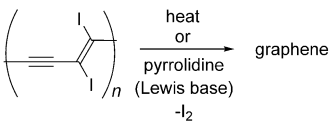

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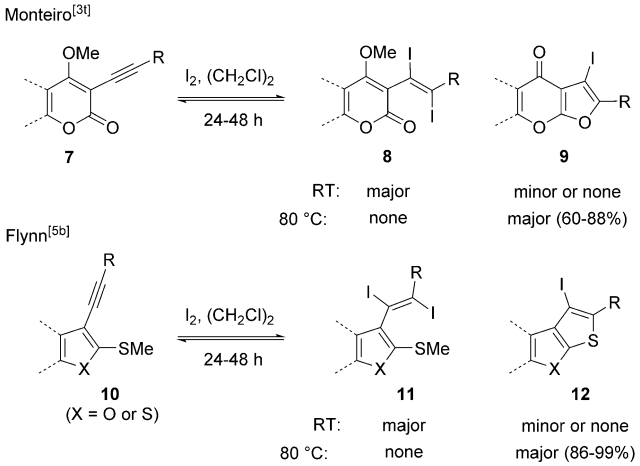
Despite the importance of the reactions of alkynes with I_2 and I^+ in synthetic chemistry, the mechanistic aspects of these classes of π-bond activation have received little attention.[10,11] Furthermore, several classes of alkynes show a resistance to iodine-mediated 5-*endo-dig* cyclization, due to the presence of deactivating substituents and/or competing I_2 addition. To overcome these challenges, we have conducted a detailed experimental and theoretical investigation of the mechanisms of alkyne activation by I_2 and iodonium reagents. Our results show that these reactions involve several parallel mechanistic pathways, the outcomes of which are determined both by the alkyne substituents and by the reagent (I_2 or IX). These findings provide guidance as to how iodocyclizations of resistant alkynes may be accomplished by a suitable choice of electrophilic reagent and conditions. Differences in the mechanisms of alkyne activation by I_2 and IX are shown to provide a means to control the 5-*exo*/6-*endo* regioselectivity.

Results and Discussion

The competition between iodocyclization and I_2 addition

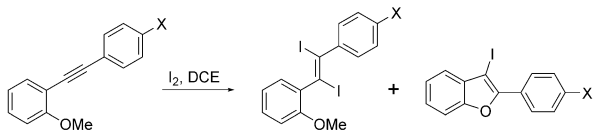
The substrate scope of many 5-*endo-dig* iodocyclizations (**1**→**2**, $n=1$) is limited by electronic effects (Scheme 1).[2b,3e,j,r–w] When R in **1** is an electron-donating group (EDG) or R′ is an electron-withdrawing group (EWG), iodocyclization is often disfavored and competing addition of I_2 or IX across the triple bond dominates instead. For alkynes in which R is an EDG, both Monteiro's group[3t] and our own laboratory[5b] have demonstrated that the resistance to iodocyclization is most effectively overcome by using I_2 as the activating reagent (Scheme 2). Thus, iodine addition predominates at room temperature (**7**→**8** and **10**→**11**) but becomes reversible upon heating to 80 °C in 1,2-dichloroethane (DCE). This enables the diiodoalkene to be irreversibly converted into the iodocyclization product (**9** or **12**). The use of I_2 for promoting iodocyclizations of electron-rich substrates has proven superior to the use of more powerful iodonium sources, which either add irreversibly to the alkyne (ICl, CF_3CO_2I, or $Pyr_2I{\cdot}BF_4$) or yield the iodocyclization product in a greatly reduced yield (e.g., *N*-iodosuccinimide (NIS) at 80 °C gave **12** in 30–40% yield).[5b]



Scheme 2. Promoting iodocyclization of resistant alkynes **1** (R = EDG) through reversible iodine addition/elimination.

We have now found that making I_2 addition reversible also allows one to achieve iodocyclizations of the second class of resistant alkynes, in which R′ is an EWG. Our chosen substrates were the 2-alkynylanisoles **13** (Table 1). Previously, Larock and co-workers observed[3j] that the treatment of the electronically unbiased alkyne **13a** with I_2 in dichloromethane gave the iodocyclization product **15a** in less than 3 h at room temperature (Table 1, entry 1), whereas the nitro-substituted analogue **13b** gave only the iodine adduct **14b**. Both reactions were reported to be performed at 0.1 M **13** and 0.15 M I_2. However, we have found that at such concentrations the addition of iodine to **13b** is very slow. A 10% conversion to **14b** was noted after 22 h (Table 1, entry 2); this increased to 21% along with trace amounts of iodocyclized product after 46 h (entry 3). When we performed the reaction under conditions previously found to give complete iodocyclization of electron-rich alkynes **7** and **10** (Scheme 2: i.e., DCE, 80 °C and 0.15 M I_2),[3t,5b] we obtained a mixture containing the starting alkyne **13b** (57%), diiodoalkene **14b** (40%) and a trace amount of iodocyclized product **15b** (3%) after 22 h (Table 1, entry 4). Further heating led to decomposition and complete conversion of **13b** to **15b** was not achieved.

Table 1. Optimization of iodocyclization of resistant alkynes **1** (R′ = EWG).



13a X = H
13b X = NO_2
13c X = CO_2Et

14a-c **15a-c**

Entry	**13** ([M])	C I_2 [M]	t	T [°C]	**13/14/15**[a]
1	**13a** (0.1)	0.15	3 h	18	0:0:100[b]
2	**13b** (0.1)	0.15	22 h	18	90:10:0
3	**13b** (0.1)	0.15	46 h	18	77:21:2
4	**13b** (0.1)	0.15	22 h	80	57:40:3
5	**13b** (0.4)	1.2	22 h	18	3:94:3
6	**13b** (0.4)	1.2	16 h	80	0:0:100[c]
7	**13c** (0.4)	1.2	70 h	18	7:31:62
8	**13c** (0.4)	1.2	15 d	18	6:5:89
9	**13c** (0.4)	1.2	22 h	80	0:0:100[d]

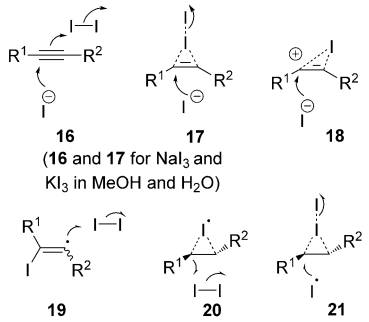
[a] Ratios determined by ^{1}H NMR spectroscopy. [b] Reference [3j]: 88% yield of the isolated product, reaction performed in dichloromethane. [c] 90% Yield of the isolated product. [d] 85% Yield of the isolated product.

A striking difference was observed when the reaction was performed at higher concentrations (0.4 M **13b** and 1.2 M I_2). Under these conditions, diiodoalkene **14b** was formed nearly quantitatively after 22 h at 18 °C (Table 1, entry 5). Heating to

80 °C led to complete conversion to **15b** (Table 1, entry 6, 90% yield of the isolated product). A similar pattern was observed with the carboethoxy derivative **13c** (Table 1, entries 7–9), in which iodocyclization could even be achieved at room temperature when the reaction was performed at high I_2 concentration (89% complete after 15 d; Table 1, entry 8). More conveniently, iodocyclization of **13c** was complete within 22 h at 80 °C (Table 1, entry 9, 85% yield of the isolated product). The rates of iodocyclization and iodine addition were similar in other solvents (toluene, CH_3CN, MeOH) to that observed in DCE.[12] Attempts to iodocyclize **13b** with NIS were not successful and only returned the starting material, even after sustained heating (80 °C, DCE, 40 h).

Proposed mechanisms for I_2 addition to alkynes

To understand the variety of conditions required for achieving iodocyclizations of different resistant substrates (Scheme 2 and Table 1), we have examined the mechanisms of iodocyclization and I_2 addition with a combination of experimental and theoretical techniques. Most prior mechanistic studies concerning the additions of iodine to alkynes have focused on reactions of propiolates in aqueous solutions containing varying ratios of I_2 and iodide salts (NaI or KI).[10a,b] These studies converged on three ionic mechanisms (Scheme 3, **16**–**18**). The dominant



Scheme 3. Previously proposed mechanisms for iodine addition to alkynes (**16**–**19**) and alkenes (**20** and **21**).

mechanism depends on the relative concentrations of I_2 and I^- and on the pH. At high iodide concentrations, the AdE_3 mechanisms **16** and **17** are favored. In **16**, nucleophilic activation of the alkyne by I^- slightly precedes engagement of the electrophilic I_2; this is preferred at low pH ($R^2 = CO_2H$). In **17**, electrophilic activation of the alkyne by iodine (I_2–alkyne complexation) promotes nucleophilic attack by I^-; this pathway is preferred at high pH ($R^2 = CO_2Na$). For reactions involving only I_2 and alkyne (no added I^-), an AdE_2 mechanism was proposed (**18**).[10b] Activation of the alkyne by an iodonium ion (following iodine solvolysis) was suggested to give an I^+–alkyne complex that undergoes nucleophilic attack by the counterion I^-. This AdE_2 pathway is supported by significant solvent (H_2O) incorporation giving α-iodoketones.[10b] Though **18** is often depicted as a symmetrically bridged iodonium cation,[2,3,10] recent calculations[11a] indicate that it is better represented as an unsymmetrical species (i.e., an iodovinyl cation), even for symmetrically substituted alkynes ($R^1 = R^2$).

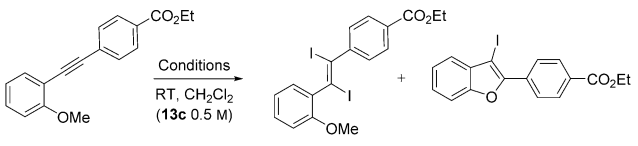
Heasley and co-workers studied iodine additions to arylethynes.[10c] They proposed that additions to this class of alkynes likely involve a radical chain process. Thus, I• (formed by homolysis of I_2) attacks the arylethyne to give an open vinyl radical **19** ($R^1 = H$, $R^2 = aryl$), which attacks I_2 to give the diiodoalkene.[10c] They were drawn to this conclusion by the lack of solvent incorporation for reactions performed in methanol; in contrast, reactions with Br_2 gave exclusively the Br/MeO adducts, presumably by an ionic pathway.

Under each of the above sets of conditions, the *trans*-diiodoalkene was formed diastereospecifically.[10,13] Although Heasley did not discuss the stereochemical implications of radical pathway **19**, we would argue that the participation of an open vinyl radical is not consistent with the exclusive formation of *trans*-diiodoalkene. In related work on additions to alkenes, the groups of Skell and Rack showed that iodine addition proceeds through a radical mechanism, at least for reactions performed under ambient light.[14] *Anti* addition and third-order kinetics were observed, leading Rack to advance two stereospecific AdE_3 mechanisms: 1) I• attacks the alkene to give a bridged radical intermediate that then attacks I_2 (**20**, also proposed by Skell), and 2) I• attacks the iodine–alkyne complex (**21**).[14b] Since iodine addition to alkynes generally gives *trans*-diiodoalkenes (*anti* addition),[13] it seems likely that if it indeed follows a radical mechanism then it would involve an alkyne equivalent of **20** or **21**, rather than open vinyl radical **19** (see also below).

Kinetic measurements

To explore the possible involvement of radicals in the additions of iodine to alkynes, we measured the rates of I_2 addition to **13c** in the light and in the dark (Table 2, entries 1 and 2). Addition was significantly faster when performed under visible light (halogen lamp) than when performed in the dark. This result suggests that iodine addition can be mediated by I•. Light versus dark had no effect on the configuration of the diiodoalkene (expected to be *trans*),[13] and did not affect the rate of io-

Table 2. Effects of light and iodide salts on iodocyclization of alkyne **13c**.

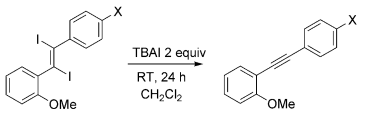


Entry	Conditions	13c/14c/15c 10 h	24 h	48 h	106 h
1	1.5 equiv I_2	92:4:4	86:6:8	80:9:11	55:22:23
2	1.5 equiv I_2 (light)	45:49:6	26:69:5	–	–
3	1.5 equiv I_2, 0.05 equiv TBAI	–	–	–	58:16:26
4	1.5 equiv I_2, 1.5 equiv TBAI	–	100:0:0	100:0:0	–
5	3.0 equiv I_2 1.5 equiv TBAI	–	97:2:1	95:2:3	–

[a] Reactions performed in the dark unless otherwise specified.

docyclization. We also investigated whether iodine addition might alternatively be catalyzed by I^- (in the dark). Small amounts of I^- (5 mol% tetrabutylammonium iodide (TBAI)) had no effect on the iodine addition rate, whereas larger quantities inhibited reaction (Table 2, entries 3–5). The same effects were observed with NaI in CH_3CN (data not shown). Presumably, the decrease in iodine addition is attributable to decreases in the concentrations of the I_2–alkyne complex and of $I^\bullet$ that result from conversion of I_2 to I_3^-. The lower electrophilicity of I_3^- compared with I_2 also accounts for the decrease in iodocyclization rate.

We also observed that TBAI efficiently promotes the elimination of I_2 from diiodoalkenes [Eq (3)]. For this reason, iodide salts may act as a useful alternative to pyrrolidine in the Lewis base-promoted conversion of polydiiododiacetylenes to conducting graphenes [Eq (2)].



14b X = NO_2
14c X = CO_2Et

13b/c
100%

(3)

Theoretical calculations

We examined the mechanisms of iodine addition and iodocyclization onto alkynes by means of density functional theory (DFT) calculations.[11,15] The calculations were performed at the M06-2X/6-311G(d,p)//B3LYP/6-31G(d)-LANL2DZ(CH_2Cl_2) level of theory, modeling the solvent (dichloromethane) with the SMD implicit model.[16] This level of theory was chosen after evaluating the performance of several functionals for reactions of relevance to I_2 addition and iodocyclization, namely, addition of I_2 to ethyne, five R–I bond homolyses, and four key steps in the reactions of alkyne **13b** with I_2. Full details are provided in the Supporting Information but the following comments may be made regarding the expected accuracy of the calculations.

The mechanisms that we consider for I_2 additions to alkynes involve elementary steps representing a wide variety of reaction types. Ionic pathways, radical pathways, and pathways involving closed-shell, polar transition states, all compete. We do not expect that DFT calculations can estimate the relative rates and thermodynamics of these reactions with quantitative accuracy. Errors arise from several sources, including: 1) The limitations in the ability of a single functional to model chemically diverse reactivity; 2) errors associated with the computation of free energies in solution, especially for ionic species; 3) certain mechanisms of I_2 addition having bimolecular rate-determining transition states, whereas others are termolecular, and 4) the concentrations of several intermediates (e.g., $I^\bullet$, I^-, and I_3^-) under experimental conditions are not known with certainty.[17] Therefore, we do not expect the DFT calculations to provide definitive mechanistic conclusions, but rather we use the calculations as a qualitative tool to support the inferences derived from our experimental studies.

Our initial calculations examined the reactions of a representative electron-poor alkyne (**13b**) with I_2, leading to either diiodoalkene **14b** or iodocyclized product **15b**. The geometries and energies of the important transition states and intermediates of these reactions are shown in Figure 1.

Four mechanisms of I_2 addition to **13b** were identified (Paths A–D).[18] In Path A, alkyne-mediated heterolysis of I_2 (**TSA**) gives the I^+–alkyne adduct **A** and I^-, the latter of which may combine with a second molecule of I_2 to give I_3^-. The I^+–alkyne adduct **A** is best described as an iodovinyl cation, not as a bridged iodonium cation. A bridged species could not be located on the potential energy surface. This is consistent with previous calculations on I^+–alkyne adducts by Yamamoto et al.,[11a] and mirrors the behavior of Br^+ and Cl^+, which generally favor open halovinyl cations relative to cyclic halonium ions.[11b,d,g] Iodovinyl cation **A** is formed regioselectively. The isomeric cation **A′** (see lower panel of Figure 1) is disfavored because the electron-poor nitrophenyl ring provides less stabilization of the positive charge compared with the anisyl ring. The bond lengths and angles of iodovinyl cations **A** and **A′** indicate that these cations both have considerable allenic character.

Paths B–D commence with formation of I_2–alkyne complex **B**. Complex **B** is computed to be 6.6 kcal mol^{-1} higher in energy than the isolated reactants (ΔG). The positive ΔG stems primarily from entropic effects; the ΔH of complexation is 0.3 kcal mol^{-1}. Following complex formation, Paths B–D differ in respect of which species attacks complex **B**. In Path B, **B** reacts with a second molecule of I_2 (**TSB**) to give ion pair [**A**]I_3, which then gives diiodoalkene **14b** plus I_2.[19] In Path C, complex **B** reacts with I^- (**TSC**) to give diiodoalkene **14b** plus I^-. In Path D, **B** reacts with $I^\bullet$ (**TSD**) to give **14b** plus $I^\bullet$.[20] The preferred site of attack differs for I^- and $I^\bullet$; I^- attacks β to the nitrophenyl ring, whereas $I^\bullet$ attacks β to the anisyl ring.

The values of $\Delta G^{\ddagger}$ for Paths A–D are 30.2, 24.3, 26.0, and 14.7 kcal mol^{-1}, respectively. Qualitatively, these values predict that the most facile mechanism of diiodoalkene formation is the radical pathway (Path D). This is consistent with our experimental observations (Table 2) that showed that I_2 addition to **13c** is accelerated by ambient light. Ionic Path C is considerably higher in energy than Path D. This result, coupled with our experimental finding that iodide salts either had no effect or inhibited I_2 addition to **13c** (Table 2), suggests that Path C is not mechanistically significant. Under typical experimental conditions, the available concentration of I^- is low, either because no iodide salt is added or because any added I^- combines with I_2 (present in excess) to form I_3^-.

If no I^- or $I^\bullet$ were present in the reaction mixture, the possible mechanisms of I_2 formation would be Paths A and B, both of which involve iodovinyl cation **A**. The barriers for these two pathways (30.2 and 24.3 kcal mol^{-1}, respectively) are lower than the barrier for iodocyclization (Path E, 31.1 kcal mol^{-1}). Experimentally, we found that I_2 addition to **13b** is kinetically favored over iodocyclization, even in the dark (Table 1, entry 5). For **13c** under similar conditions (Table 2, entry 1), iodocyclization has about the same rate as I_2 addition. In view of these observations, we cannot rule out the involvement of Path A or Path B. Path A is first order in I_2, whereas Paths B and D are second order in I_2. However, even in the dark, where photoin-

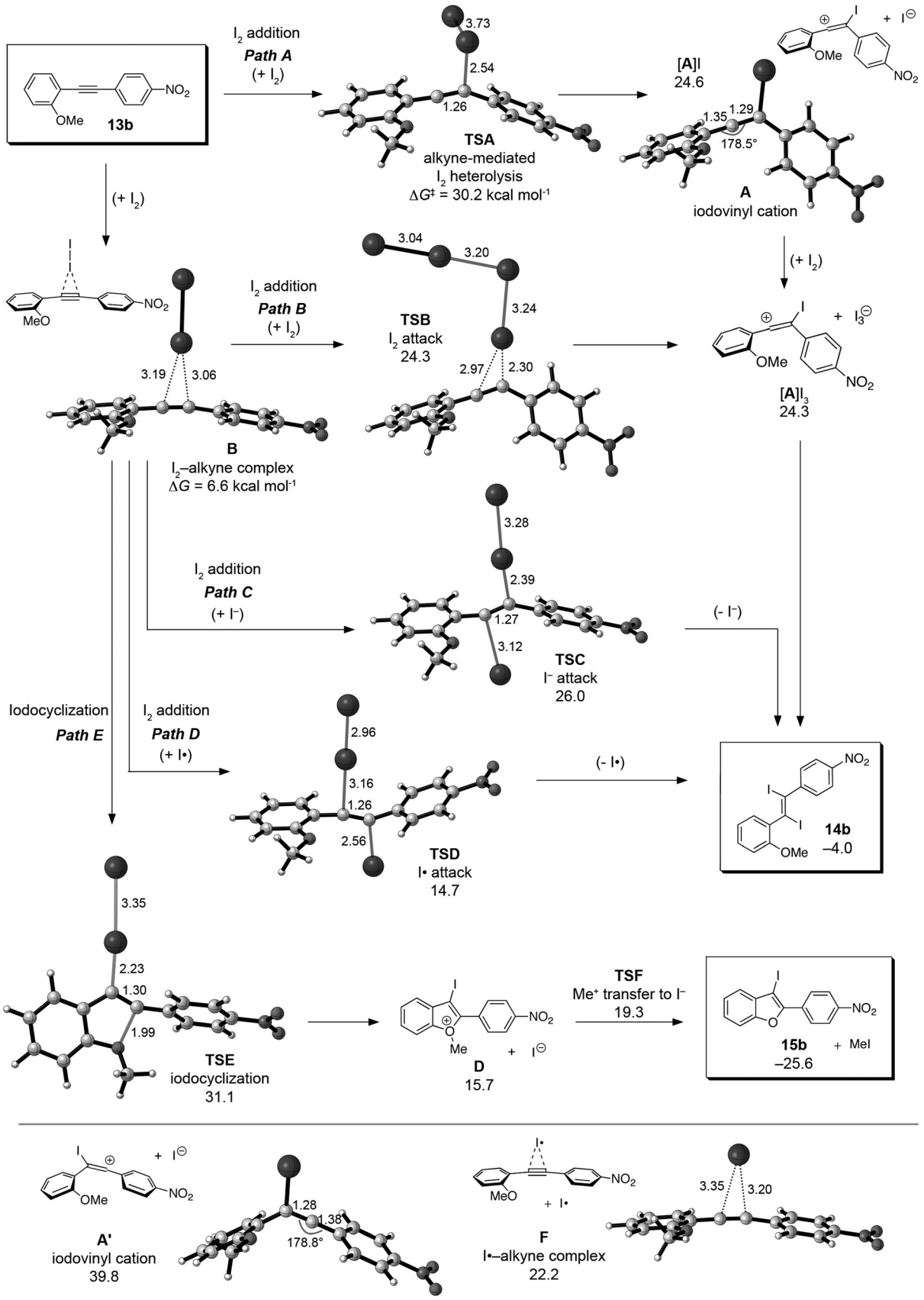


Figure 1. Mechanisms of iodine addition (Paths A–D) and iodocyclization (Path E) for electron-deficient alkyne **13b** in dichloromethane, computed at the M06-2X/6-311G(d,p)//B3LYP/6-31G(d)-LANL2DZ(CH_2Cl_2) level of theory. Distances in Å, ΔG in kcal mol^{-1}.

duced homolysis of I_2 is suppressed, there is still likely to be a non-negligible concentration of I•, due to thermal homolysis of I_2 (or of **B**).[21] These trace quantities of I• would catalyze the addition of I_2 to **13b**/**c**. In the light, the concentration of I• would be much higher. Therefore, we propose that the dominant mechanism of I_2 addition to electron-poor alkynes such as **13b** and **13c** both in the light and in the dark is the I•-mediated pathway, Path D.

The predicted mechanism of iodocyclization of **13b** is Path E. This involves intramolecular nucleophilic attack on I_2–alkyne complex **B**. In principle, an alternative mechanism of iodocyclization could involve intramolecular nucleophilic attack in iodovinyl cation **A**′. However, the very high energy of **A**′ (40 kcal mol^{-1}) makes such a mechanism unlikely.

The calculations correctly predict the observed thermodynamic and kinetic products of the reaction of **13b** with I_2. Experimentally, diiodoalkene **14b** is the kinetic product and iodocyclized product **15b** is the thermodynamic product (Table 1). In the calculations, I_2 addition through Path C is the kinetically favored process, with $\Delta G^{\ddagger} = 14.7$ kcal mol^{-1} (provided that homolysis of I_2 is not rate-limiting) and an overall ΔG of −4.0 kcal mol^{-1}. Iodocyclization (Path E) has a higher barrier (31.1 kcal mol^{-1}) but is thermodynamically favored (−25.6 kcal mol^{-1}).

Analogous calculations were performed for I_2 addition and iodocyclization onto electron-rich alkyne **10a** (Figure 2). Compared with the electron-poor alkyne **13b**, the main difference in the mechanistic picture for **10a** is that the ionic pathways involving iodovinyl cation (Paths A and B) are significantly more facile for **10a**. The barriers for these two pathways drop by 6–13 kcal mol^{-1} on going from **13b** to **10a**, such that they now lie only 2–3 kcal mol^{-1} above radical Path D. Taking into account the expected degree of accuracy of the calculations, it appears likely that iodovinyl cation formation plays an important role in the reactions of **10a**.

Furthermore, the calculations indicate that the participation of an iodovinyl cation is consistent with the observed stereoselectivity of addition. Experimentally, only a single isomer of diiodoalkene is obtained, assumed to be *trans*.[13] Calculations predict that addition of I^- to **G** on the side *syn* to phenyl (leading to *trans* diiodoalkene **11a**) has a 4 kcal mol^{-1} lower barrier than addition *syn* to the iodo substituent leading to the *cis* isomer (see the Supporting Information). By contrast, I• attack on I_2–alkyne complex **H** (Path D) is necessarily stereospecific, giving the *trans* diiodoalkene. Thus, Paths A, B, and D are all predicted to lead exclusively to the *trans* isomer of diiodoalkene **11a**, consistent with the experimental result.[22]

As with electron-poor alkyne **13b**, iodocyclization of **10a** occurs most readily through Path E. The alternative mechanism for iodocyclization, involving iodovinyl cation **G**′, is high in energy (see **TSK** and **TSL**). In agreement with the experiment, the calculations predict that the kinetic product of the reaction of **10a** with I_2 is diiodoalkene **11a** and the thermodynamic product is iodocyclized compound **12a**.

The predicted importance of ionic pathways for I_2 addition to **10a**, but not for **13b**, is consistent with the experimental observation that electron-rich alkynes undergo iodine addition much faster than do electron-deficient alkynes (in the dark). Electron-donating substituents render I_2 addition facile enough to proceed at room temperature. For example, the treatment of **10a** with 1.0 equivalent of iodine (0.2 M in DCE) gave >50% conversion to diiodoalkene **11a** in <0.5 h at 18 °C (data not shown), compared with 10% conversion after 22 h at 18 °C for **13b** (Table 1, entry 2). For **10a**, Paths A, B, and D each become reversible upon heating, allowing thermally-induced conversion of diiodoalkene back to alkyne plus I_2 (or I_2–alkyne complex **H**), followed by iodocyclization.

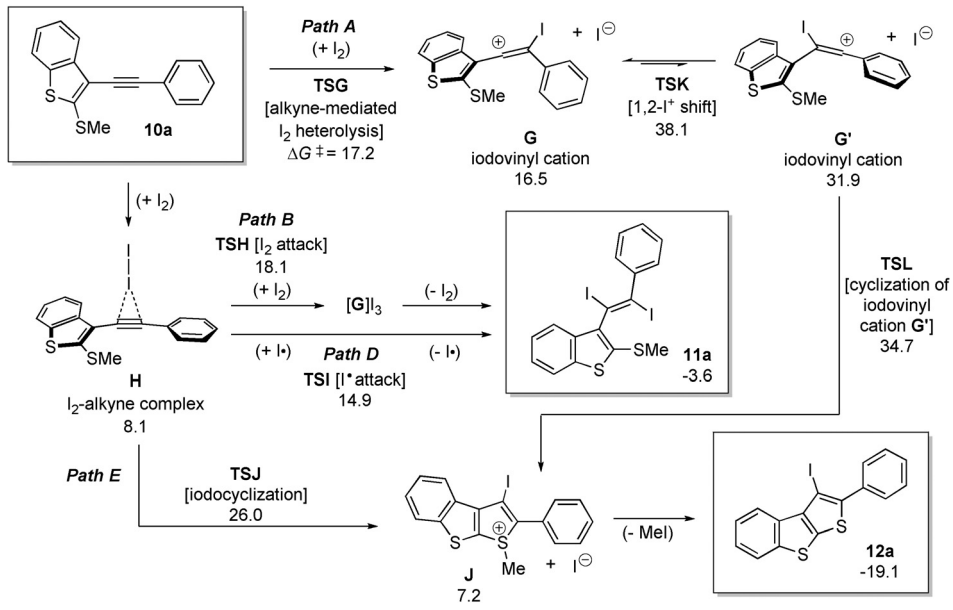
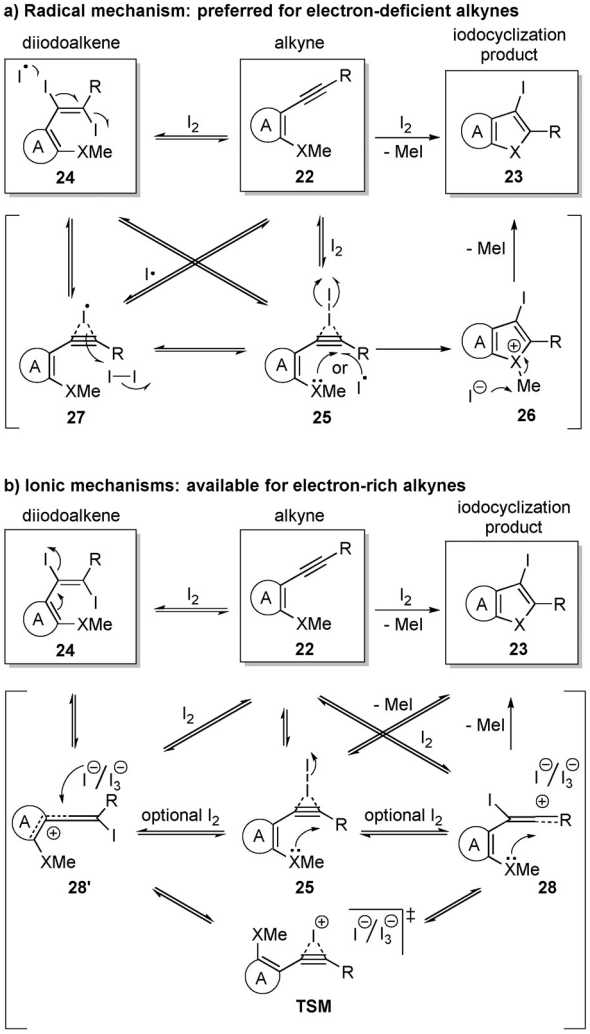


Figure 2. Mechanisms of iodine addition and iodocyclization for electron-rich alkyne **10a**, computed at the M06-2X/6-311G(d,p)//B3LYP/6-31G(d)-LANL2DZ(CH_2Cl_2) level of theory. ΔG in kcal mol^{-1}.

Implications for the competition between I_2 addition and iodocyclization

In light of our kinetic measurements and theoretical studies, we propose two general mechanistic scenarios for the competition between iodine addition and iodocyclization onto alkynes (Scheme 4). For electron-deficient alkynes, we propose that iodine addition proceeds primarily through a radical chain mechanism (**25**, **27**), resembling the pathways proposed by Skell and Rack for analogous reactions of alkenes (**20** and **21**, Scheme 3). Catalytic I• may arise from homolysis of I_2 and/or



Scheme 4. Proposed mechanisms of iodocyclization and iodine addition onto different classes of alkynes.

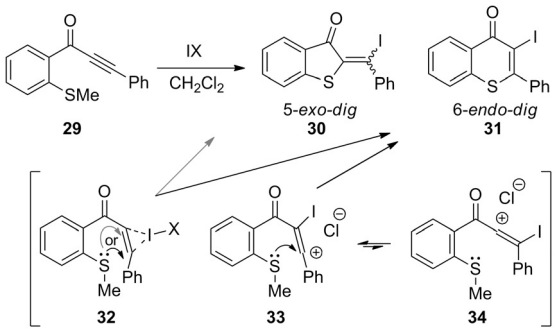
homolysis of the I_2–alkyne complex **25** to give **27**. Notably, the calculations predict that the I–I bond in I_2–alkyne complex **B** (Figure 1) is 6 kcal mol^{-1} weaker with respect to homolysis than that of I_2 itself.[21] Irrespective of the source of I$^{\bullet}$, attack on the I_2–alkyne complex **25** gives *trans*-diiodoalkene **24** stereospecifically. Alternatively, but less favorably, I$^{\bullet}$ addition to the alkyne gives the bridged radical **27**, which reacts with I_2 through the same transition state as **25** + I$^{\bullet}$ to give the same product, **24**. The AdE_3 nature of both pathways (**22**→**25**→**24** and **22**→**27**→**24**) accounts for the observation that at room temperature in the dark, in which the I$^{\bullet}$ concentration is smallest, the rate of addition is sensitive to I_2 concentration. The termolecular reaction of alkyne with $2\times I_2$ (Path B, Figure 1) may also play a minor role.

For electron-deficient alkynes (**1**, R = EWG), the rate of nucleophilic attack by XMe is slower than I$^{\bullet}$-catalyzed iodine addition, even in the dark (compare **TSD** and **TSE**, Figure 1). Heating accelerates homolysis of I_2 and/or **25** to give I$^{\bullet}$, causing the iodine addition reaction to become rapidly reversible and providing sustained access to **25**, as well as overcoming the thermal barrier to iodocyclization **25**→**26**. A high concentration of I_2 is also important for iodocyclization because it affords an elevated concentration of **25**. This is especially true at high temperature, in which complexation is entropically disfavored (Table 1, compare entries 4 and 6).

For electron-rich alkynes (**22**, A-ring and/or R = EDG), we propose that radical reactions still provide the lowest-energy mechanism of I_2 addition, but pathways involving iodovinyl cations also become important: That is, either alkyne-mediated heterolysis of I_2 or attack by I_2 on the I_2–alkyne complex, giving iodovinyl cations **28** and **28′**. Interconversion between **28** and **28′** may involve reversion to I_2–alkyne complex **25** and/or alkyne + I_2, or, alternatively, a direct 1,2-I$^+$ shift through transition state **TSM**. Cation **28** is favored when R is more electron-donating than the A-ring, and vice versa for **28′**. Cation **28** favors cyclization to **23**, whereas **28′** favors reaction with I$^-$ to give **24**. For substrates that favor I_2 addition over iodocyclization (i.e., **22**, A-ring = EDG), higher temperatures cause the I_2 addition reaction to become reversible, by promoting thermal heterolysis of **24** to **28′**. This affords sustained access to **25** and/or **28** (in equilibrium with **28′**), either of which may undergo iodocyclization. For these alkynes, high I_2 concentrations are not necessary to effect iodocyclization. This can be attributed to 1) the unimolecular nature of heterolysis of **24** that leads to re-formation of **28′**, and 2) the higher nucleophilicity of the alkyne, which favors reaction of **22** (A-ring = EDG) with iodine to give **28** or **25** from which iodocyclization can occur.

endo/*exo* Selectivity

Further experimental support for the intermediacy of geometrically distinct I_2–alkyne (symmetrical) and iodovinyl (unsymmetrical) intermediates is provided by the *exo*/*endo* selectivities of iodocyclizations involving 1-(2-(methylthio)phenyl)propynones **29** (Scheme 5). We previously reported that the reactions of various analogues of **29** with I_2 favor *5-exo* products **30**,[4a] whereas Larock et al. subsequently reported that ICl gives exclusively *6-endo* products.[3k] We have reinvestigated



IX	30[a]	31[a]
I_2	80 (78%)[b]	20 (18%)
ICl	<1	>99 (69%)

Scheme 5. *endo*/*exo* Selectivities of iodocyclizations of resistant alkynes **29**. [a] Ratio determined by using ^{1}H NMR spectroscopy (yield of the isolated product in parentheses). [b] Isolated as an *E*/*Z* mixture.

this reaction by treating **29** with both I_2 and ICl in dichloromethane (Scheme 5). As previously reported,[3k,4a] treatment with I_2 favored the *exo*-isomer **30**, whereas ICl gave exclusively the *endo*-isomer **31**.[23] Differences in the dominant reactive intermediate as a function of reagent explain these results. For I_2, the bridged intermediate **32** is formed, which can cyclize by either the *exo*- or *endo*-pathway and shows modest selectivity for the *exo*-isomer **30**.[24] On the other hand, ICl acts as an iodonium source that gives essentially exclusive formation of the more stabilized iodovinyl cation **33** relative to **34** and thus strongly favors the *endo*-product **31**. A broader examination of the scope of this *exo/endo* divergence is currently underway.

Conclusion

Kinetic and theoretical studies provide new insights into the mechanistic features responsible for the different outcomes of iodocyclizations involving I_2 and iodonium reagents. Thus, iodocyclizations mediated by I_2 generally involve a relatively symmetrical I_2–alkyne complex, whereas iodocyclizations mediated by iodonium reagents involve (unsymmetrical) iodovinyl cations and in this respect resemble the reactions of Br_2 and Cl_2 more closely. Any unfavorable electronic effects associated with the alkyne substituents tend to be mitigated in reactions mediated by I_2, because the I_2–alkyne complex is relatively symmetrical and capable of activating both carbons to nucleophilic attack. In contrast, in reactions mediated by iodonium reagents, undesired reactivity is traced to the formation of the undesired regioisomer of iodovinyl cation intermediate. These differences are demonstrated by the superior capacity of I_2 to promote *5-endo-dig* iodocyclizations of resistant alkynes **22** (R = EWG or A = EDG) and by the abilities of I_2 and I^+ to play complementary roles in the *endo/exo*-divergent iodocyclizations of polarized alkynes such as **29**. The mechanistic insights about the differing roles of I_2, $I^{\bullet}$, I^+ and I^- in alkyne activation reported herein should facilitate the further development of reaction classes involving this chemistry, having broad implications for organic synthesis.

Experimental Section

All experimental and computational details can be found in the Supporting Information, which includes compound preparation and characterization, copies of spectra of new compounds, theoretical benchmarking for I_2 additions and iodocyclizations, and computed geometries and energies.

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Keywords: alkynes · cyclization · density functional calculations · iodine · synthetic methods

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[19] For a related mechanistic proposal involving alkenes, see: P. W. Robertson, J. B. Butchers, R. A. Durham, W. B. Healy, J. K. Heyes, J. K. Johannesson, D. A. Tait, *J. Chem. Soc.* **1950**, 2191.

[20] No open vinyl radical (**19**) could be located: Attempts to optimize this species led instead to the van der Waals complex **F**. A similar result was obtained with B3LYP-D3: Attempted optimization of the vinylic radical PhC(I)=C(•)Ph with B3LYP-D3 led only to the van der Waals complex of PhCCPh and I•.

[21] Homolysis of I_2 is computed to have $\Delta G = 21.8$ kcal mol^{-1}. The computed ΔG for homolysis of the I–I bond in **B** is 15.6 kcal mol^{-1}. For **H**, the corresponding value is 10.5 kcal mol^{-1}.

[22] *trans*-Diiodoalkene **11a** is 2 kcal mol^{-1} more stable than the corresponding *cis* isomer (see the Supporting Information).

[23] Compound **30** was initially formed as a single isomer (presumably the *E* isomer), which isomerized to an *E/Z* mixture upon work-up and chromatography.

[24] Consistent with this idea, computations predict that *exo* cyclization in **32** (X = I) is favored by 2.8 kcal mol^{-1} ($\Delta\Delta G^{\ddagger}$) over *endo* cyclization (see the Supporting Information).

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