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Nucleophilic Addition to a *p*-Benzyne Derived from an Enediyne: A New Mechanism for Halide Incorporation into Biomolecules

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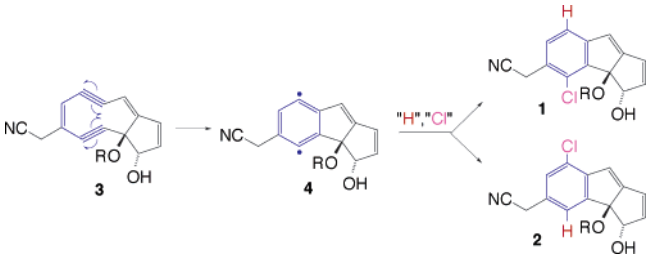
Abstract: Biosynthesis of haloaromatics ordinarily occurs by *electrophilic* attack of an activated halogen species on an electron-rich aromatic ring. We now present the discovery of a new reaction whereby a *nucleophilic* halide anion can be attached even to an aromatic ring without activating substituents. We show that the enediyne cyclodeca-1,5-diyn-3-ene, in the presence of lithium halide and a weak acid, is converted to 1-halotetrahydronaphthalene. The kinetics are consistent with rate-limiting cyclization to a *p*-benzyne biradical that rapidly adds halide and is then protonated. This reaction has interesting mechanistic features and important implications for incorporation of halide into biomolecules.

Introduction

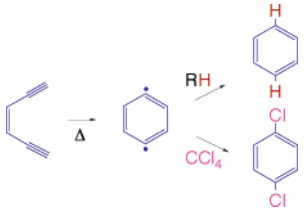
Naturally occurring haloorganics have long attracted attention, owing to their medicinal properties and to the fascinating machinery employed by nature for their biosynthesis.[1] Incorporation of halogen ordinarily occurs by nucleophilic substitution at a saturated carbon or by electrophilic substitution onto an electron-rich aromatic ring through the action of a haloperoxidase or halogenase.[2] Notable examples include the biosyntheses of tetraiodothyronine and chlortetracycline, which are formed via the actions of heme-iron haloperoxidase and flavin-dependent halogenase, respectively. We now propose a new mechanism for the incorporation of ubiquitous halide anions onto a *p*-benzyne biradical. We find that heating an enediyne in the presence of halides does indeed produce haloaromatics, and the kinetics are consistent with reaction via a *p*-benzyne intermediate.

The recent isolation of two pairs of marine natural products, sporolides A/B and cyanosporasides A/B,[3] now leads us to propose a mechanism for the *direct* incorporation of halide *without* its conversion to an electrophile. The latter (**1**, **2**) were isolated as a 1:1 mixture of positional isomers (Scheme 1). They are related by the unusual feature of a chlorine atom at either of two aromatic positions, but not both. It was suggested[3b] that these are derived from an enediyne precursor (**3**) that cyclizes to a *p*-benzyne biradical (**4**). However, the source of the chlorine atom was a mystery, as was the source of bromine in two analogs. We now propose that the halogen is introduced as halide, and we test this with a model enediyne.

Scheme 1. Proposed (Partial) Mechanism for Formation of Cyanosporasides (**1**, **2**; R = 3-oxo-4-methyl-β-fucosyl) from an Enediyne Precursor, **3**



Scheme 2. Atom Abstraction Chemistry of *p*-Benzyne



Enediynes have aroused much interest because of their antibiotic activity.[4] They act by cyclizing to a *p*-benzyne, as was observed by Bergman in simpler enediynes.[5] Control over the cyclization has been sought extensively.[6] The *p*-benzyne can abstract either hydrogen or halogen atoms from organic molecules such as 1,4-cyclohexadiene or CCl_4 (Scheme 2). Hydrogen atom abstraction from DNA leads to double-strand cleavage, and this is the basis for the action of Gemtuzumab ozogamicin (Mylotarg), which has been approved for treatment of acute myeloid leukemia.[7] However, there is no known case where one halogen and one hydrogen are introduced. The closest

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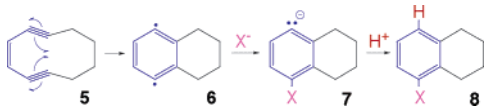
10.1021/ja070023e CCC: $37.00

Scheme 3. Proposed (Complete) Mechanism for Haloaromatic Formation via Halide Addition to a *p*-Benzyne Derived from an Enediyne



is where one molecule of the spin-trapping reagent phenyl *tert*-butyl nitrone is added along with one hydrogen atom from *β*-mercaptoethanol.[8]

To explain the unusual incorporation of hydrogen and chlorine in **1** and **2** we here propose attack of halide on a *p*-benzyne to generate a haloaryl anion that is trapped in situ by a proton donor. For our studies we used cyclodeca-1,5-diyn-3-ene (**5**).[9] Its 10-membered ring has sufficient strain that cyclization to a *p*-benzyne (**6**) occurs at a convenient rate on slight heating. Nucleophilic attack by halide on **6** can then lead to a haloaryl anion (**7**, X = Cl, Br, I, or the corresponding aryllithium), which is readily protonated to give 1-halotetrahydronaphthalene (**8**), as proposed in Scheme 3.

We now show that heating **5** in the presence of halide anion and an acid does indeed produce **8** (X = Cl, Br, I) and that the kinetics are consistent with **6** as the intermediate that is captured by halide. Moreover, this mechanism can account for the 1:1 mixtures and for the single chlorine in enediyne-derived natural products such as **1** and **2**.

Experimental Section

Sample Preparation. Cyclodeca-1,5-diyn-3-ene (**5**) was synthesized by a standard procedure.[10] It was added to a solution of lithium halide in wet DMSO-d_6 containing an aliquot of 1,3,5-trichlorobenzene as internal standard. Because formation of halotetralin (**8**) consumes HX, the reaction produces an equivalent of base, which would complicate the reaction by functioning as another nucleophile. To avoid this and establish buffered conditions once the reaction starts, a carboxylic acid (acetic or pivalic) was included. No effort was made to remove water from the solvent, inasmuch as the carboxylic acid also hydrogen-bonds to the halide. The sample in an NMR tube was degassed by freeze/pump/thaw on a Schlenk line, sealed, and then immersed in a 37 °C (±0.1 °C) oil bath. Disappearance of starting material and formation of product were monitored periodically by removing the sample and analyzing it by NMR and after ~80 h by mass spectrometry.

NMR spectra were obtained on a Varian 500 MHz UNITY spectrometer. GC−mass spectra were obtained on a Thermo-Finnigan Trace GC/MS Plus.

Characterization of Products. 1-Chloro-5,6,7,8-tetrahydronaphthalene: ^{1}H NMR (DMSO-d_6) δ 1.67 (2H, m, $CH_2CH_2CH_2CH_2$), 1.73 (2H, m, $CH_2CH_2CH_2CH_2$), 2.64 (2H, t, J = 6.5, $CH_2CH_2CH_2CH_2$), 2.70 (2H, t, J = 6.0, $CH_2CH_2CH_2CH_2$), 7.00 (<1H), 7.05 (1H, d, J = 7.5 Hz), 7.15 (1H, d, J = 8 Hz). GC−MS (EI) m/z calcd for $C_{10}H_{10}ClD$ (M^+): 167.2; found 167.2, plus peaks at M + 2 and M − 1 (incompletely deuterated).

1-Bromo-5,6,7,8-tetrahydronaphthalene: ^{1}H NMR (DMSO-d_6) δ 1.65 (2H, m, $CH_2CH_2CH_2CH_2$), 1.72 (2H, m, $CH_2CH_2CH_2CH_2$), 2.60 (2H, t, J = 6.5, $CH_2CH_2CH_2CH_2$), 2.69 (2H, t, J = 6.0, $CH_2CH_2CH_2CH_2$), 6.98 (1H, m), 7.04 (<1H, d, J = 8 Hz), 7.32 (1H, d, J = 8 Hz). GC− MS (EI) m/z calcd for $C_{10}H_{11}Br$ (M^+): 210.0; found 210.0, plus peaks at M + 2 and M + 1 (partially deuterated).

1-Iodo-5,6,7,8-tetrahydronaphthalene: ^{1}H NMR (DMSO-d_6) δ 1.61 (2H, m, $CH_2CH_2CH_2CH_2$), 1.70 (2H, m, $CH_2CH_2CH_2CH_2$), 2.51 (2H, t, J = 7.0, $CH_2CH_2CH_2CH_2$), 2.65 (2H, t, J = 6.0, $CH_2CH_2CH_2CH_2$), 6.81 (1H, m), 7.05 (<1H, d, J = 7.5 Hz), 7.60 (1H, d, J = 7 Hz). GC−MS (EI) m/z calcd for $C_{10}H_{11}I$ (M^+): 258.0; found 258.1, plus peak at M + 1 (partially deuterated).

Kinetics. All studies were done in pairs that differed in only one variable. Besides an initial ^{1}H NMR spectrum each sample was analyzed at intervals, until ≤5% of starting material remained. The time to remove the sample and acquire each spectrum was 10−20 min, which was subtracted from the time elapsed.

Disappearance of starting material was monitored by comparing the integrated intensity of the olefinic CH singlet of the enediyne (δ 5.88) to that of 1,3,5-trichlorobenzene (δ 7.61) as internal standard. The first-order rate constant k was obtained from a logarithmic plot of [enediyne] versus time. Nonlinear fitting to exponential decay gave nearly the same values. Deviations from first-order kinetics were not explored for reactions without added halide.

Yields. Percent yields of product were obtained from the ^{1}H NMR integrations of product signals at the last time point, relative to internal standard. They are reported as percent conversions, relative to the amount of reactant consumed, under conditions where >90% was consumed. One of the product doublets was often weaker than the other two signals, especially when the reaction was carried out with D_2O (which exchanges with the pivalic acid). This was due to deuterium incorporation, which could be confirmed by GC−MS analysis, as noted in the characterizations above. Those weaker signals were not used for the analysis of product yields. With LiBr or LiCl yields were instead based on the intensity of the most downfield doublet. With LiI this overlapped with the internal standard, so the product CH_2 intensity at δ 2.65 was compared to the pivalic acid intensity at δ 2.35. Owing to errors in integration, the accuracy of the percent yields is generally ±4.

Computations. Ab initio density functional theory calculations on the energy of interaction between *p*-benzyne (**9**) and F^-, Cl^-, OH^-, or H_2O were performed at the B3LYP/6-31G(d,p) level using Gaussian 98, revision A.7.[11] Basis-set superposition error was ignored.

Results

When a solution of **5** in DMSO-d_6 at 37 °C is monitored by ^{1}H NMR, the olefinic CH singlet at δ 5.88 slowly disappears. In the presence of excess lithium halide plus excess weak acid three new signals appear between δ 7.0 and 7.2 (Cl), 7.0 and 7.35 (Br), or 6.8 and 7.6 (I). In addition, the two CH_2 signals of **5** separate into two pairs of signals, indicating a symmetry reduction, which excludes **8** (X = H), the usual product from **6**.[5] Figure S1 in the Supporting Information shows representative ^{1}H NMR spectra in the presence of LiBr. GC−MS analysis showed volatiles with m/z corresponding to $M^+ = C_{10}H_{10}ClD$, $C_{10}H_{11}Br$, or $C_{10}H_{11}I$. Therefore, the product is the 1-halotetrahydronaphthalene (**8**, X = Cl, Br, or I).

According to both ^{1}H NMR integration and GC−MS analysis, **8** is partially deuterated at C4. Even without added D_2O there is deuterium incorporation, from DMSO-d_6. Percent deuterium enrichments in **8** (X = Cl, Br, I) were found to be 67%, 51%, and 42%, respectively, by ^{1}H NMR spectroscopy and 60%, 44%, and 40% by GC−MS analysis. The increasing extent of deuteration, from I to Br to Cl is such that **8** (X = Cl) has

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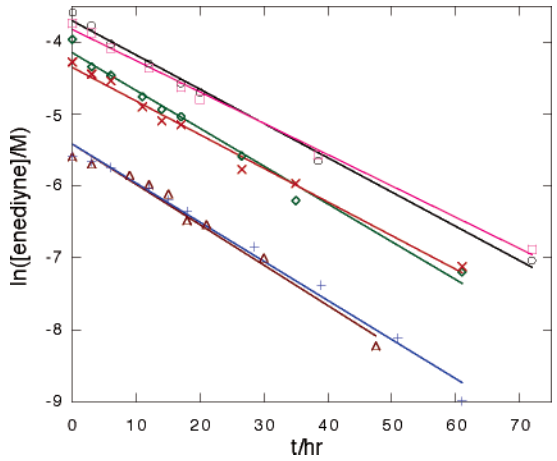

Figure 1. Plot of ln[enediyne] vs time for reaction of **5** with LiBr under conditions of entries 6−11 in Table 1 (+, ◇, △, ×, ○, and □, respectively).

Table 1. Rate Constants and Yields of **8** (X = Cl, Br, I) for Reactions of Enediyne **5** with Halide and Pivalic Acid in DMSO-d_6 at 37 °C

MX	$[\mathbf{5}]_o$/mM	$[X^-]$/mM	[HA]/mM	$10^5 k/s^{-1}$	%yield
LiI	75	750	90	1.42	100
LiI[a]	4	550	20	1.38	100
LiI	4	55	20	1.31	100
LiI	75	370	90	1.35	98
LiI[b]	4	550	20	1.23	55
LiBr	3.8	550	15	1.51	100
LiBr	19	576	20	1.46	100
LiBr[a]	3.8	550	15	1.56	92
LiBr[a]	14	584	20	1.30	92
LiBr	24	360	190	1.21	77
LiBr	28	420	84	1.32	71
LiCl	3.8	550	15	1.30	99
LiCl[a]	3.8	550	15	1.59	37
none	15.5	0	0	2.07	0

[a] + 20% D_2O. [b] + 50% D_2O.

incorporated more than 0.5 deuterium atoms, as expressed in the characterizations above.

Table 1 summarizes the kinetic data. The average rate constant is (1.38 ± 0.12) × 10^{-5} s^{-1}, even though the concentrations of enediyne, halide, and acid vary more than 10-fold. Figure 1 shows such plots for six different conditions of excess bromide. Slopes are clearly the same for all.

Some samples deposited a flocculent yellow material, especially at higher concentrations of **5**. Upon isolation and dissolution in $CDCl_3$, it showed no ^1H NMR signals, consistent with a polymer that tumbles slowly, as had been observed from other enediynes.[12] GPC analysis indicated a weight-average molecular mass of 21 kDa. Data from experiments at high [enediyne], where polymerization complicates the reaction, have therefore been excluded from Table 1. One entry without added halide, which was not used in evaluating the average *k*, illustrates a faster disappearance of **5**.

Yields are included in Table 1. They often reach 100%, especially at low [enediyne]. A quantitative yield of a single product is rare and perhaps unique in *p*-benzyne chemistry, owing to polymerization;[13] indeed, only 55% **8** (X = H) was obtained earlier from **5**.[9]

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Table 2. Energetics (kJ/mol) of Nucleophilic Addition to *p*-Benzyne (**9**), to Form an Aryl Anion

nucleophile	$-\Delta H^{0\,a}$	$-\Delta G^{0\,b}$	$-\Delta E^c$
F^-	274	104	550
Cl^-	128	84	216
Br^-	103	81	
I^-	84	101	
OH^-			570
H_2O			−35

[a] Experimental, gas-phase. [b] Experimental, aqueous. [c] Calculated, gas-phase.

Thermodynamic Data. Table 2 lists ΔH^0, the standard (gas-phase) enthalpies of halide additions to *p*-benzyne (**9**), ΔG^0, the standard free energies of halide additions to **9** in water at 25 °C, and ΔE, the B3LYP-calculated gas-phase energies of nucleophilic addition to **9**. The data show that the halide additions of Scheme 3 are all very exothermic and favorable thermodynamically even in water. The published data used to derive these values, and their sources, are described in the Supporting Information.

Discussion and Conclusions

How is **8** formed? The key result is that the rate is independent of the concentration of acid or halide and regardless of which halide is present. Thus, the rate law is given simply as eq 1. It follows that the rate-limiting step is the cycloaromatization of **5** to form the *p*-benzyne **6**, which then rapidly proceeds to product. This is the same logic as was applied to hydrogen atom donors in the rearrangement of two bicyclic enediynes.[14]

$$-\mathrm{d[enediyne]}/\mathrm{d}t = k\mathrm{[enediyne]} \qquad (1)$$

Alternative mechanisms can be excluded. The reaction is definitely not first order in X^-, nor in acid, which is the source of the hydrogen at C4. This excludes the direct addition of HX across the triple bonds, as in *o*-bis(ethynyl)benzene,[15] as well as nucleophilic addition to the enediyne.[16] Nor can the mechanism involve reversible protonation of **5**, followed by rate-limiting cyclization to a phenyl cation, because this would require the rate to depend on acidity and also to deviate from first-order kinetics as reaction depletes acid. Nor can the mechanism involve retrocyclization of **6** to 1,2-diethynylcyclohexene,[17] followed by protonation or halide addition, because this too would be first order in acid or halide. Electron transfer from X^- to *p*-benzyne can also be rejected, because it is endothermic by >170 kJ mol^{-1}.[18] Electron transfer to **5**, as in cyclization of some cross-conjugated enediynes,[19] is even more unfavorable. Finally, a reversal of the order of nucleophilic addition and protonation in Scheme 3 can be excluded by the observation of deuterium incorporation from DMSO-d_6, which is a sufficiently strong acid to trap the aryl anion but would not

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Scheme 4. Detailed Mechanism of Halide Addition to *p*-Benzyne **9**

convert the *p*-benzyne to a phenyl cation. We therefore assert Scheme 3 as the mechanism of this reaction.

The biradical nature of a *p*-benzyne (**9**) raises further questions of mechanism and transition-state structure (Scheme 4). Exactly how does **6** lead to **8**? "Electron pushing", as in **10**, is a unique mix of transfers of an electron pair and a single electron. The transition state implied by **11** is more informative. Because the biradical is a singlet, with two electrons of opposite spin, those electrons can pair in one σ orbital while the electron pair from X^- is transferred to the other σ orbital. Alternatively, those two paired electrons may be viewed as forming a weak σ bond (strictly, a σ antibond)[20] between carbons 1 and 4, as in **12**, and the reaction is a nucleophilic displacement of C4 as leaving group. This addition is then quite different from the nucleophilic additions to the genuine sigma bonds of *o*-benzynes or of butalene, or to a cationic *m*-benzyne in the gas phase.[21a,22] It is the reverse of the collision-induced decomposition that generates *p*-benzyne in the gas phase,[23] and a nonradical pathway was proposed for addition of 3-fluoropyridine to a cationic *p*-benzyne in the gas phase.[24]

The immediate precursor of **8** is the haloaryl anion **7**. This is a strong base that can abstract a proton from any acid, but it cannot accept a second halide. The contrast between the reactivities of *p*-benzyne **6** and anion **7** accounts for the incorporation of one halide and one proton. This differs from radical reactions of a *p*-benzyne, whereby hydrogen or halogen can be added in either step.

It is informative to compare the halide addition of Schemes 3 and 4 to one of the steps in $S_{RN}1$ substitution (eq 2).[21b] This addition to an aryl radical is energetically favorable with strong nucleophiles, but not with halide,[25] whose addition is further retarded by an intrinsic barrier. Addition of X^- to biradical **9** might appear to be even more unfavorable, as with addition of hydrogen atoms.[26]

$$Ar^{\bullet} + Nu^- \rightarrow ArNu^{\bullet -} \qquad (2)$$

Nevertheless, the thermodynamic data in Table 2 show that halide addition to *p*-benzyne is exothermic, not only in the gas phase, but also in water. Moreover, the computed energy of interaction between Cl^- and **9** (in the gas phase) shows no activation barrier, as can be seen from Figure S2 in the Supporting Information. This ignores the necessity of desolvating the ion, which does create a barrier.

The unfavorability of the addition in eq 2 is due to the extra electron of $ArX^{\bullet -}$, which must be in a high-energy π^* or σ^* orbital, whereas the electron pair of Ar^- is in a σ orbital. Furthermore, an intrinsic barrier can arise from the transfer of a σ electron in $Ar^{\bullet}$ to a π^* electron in $ArX^{\bullet -}$,[27] whereas in the addition to *p*-benzyne an electron is readily transferred from one σ orbital into another, where two electrons pair, as in **11**.

In competition experiments, Br^- is 20 times as reactive toward **6** as Cl^-, but 1,4-cyclohexadiene traps **6** 2.5 times as well as Br^- adds. These results are evidence for the role of solvation in creating a barrier to halide addition, which is ignored in Table 2 and Figure S2. Indeed, the data in Table 1 show small variations due to polymerization, which competes with halide addition to **6**, especially for Cl^- and with added water. Without any added halide the rate constant for disappearance of **5** is clearly higher, owing to polymerization.

The variations in the extent of deuterium incorporation represent an interesting manifestation of selectivity in the reactions of aryl anion **7**. The deuterium content of **8** is observed to increase from X = I to Br to Cl. In the absence of added D_2O, the source of that deuterium is DMSO-d_6. The fact that DMSO-d_6 can compete with pivalic acid demonstrates that the species that reacts is a very strong base. This is evidence that the intermediate that is trapped by acid is an aryl anion (or aryllithium), which is unselective toward acids. The variations with halide are too large to be due to substituent effects of halogens on the basicity and selectivity of the para lone pair in **7**. Instead, we infer that the variations arise indirectly, through hydrogen bonding of X^- to the pivalic acid. This reduces its reactivity, relative to that of DMSO-d_6. Because hydrogen bonding increases from I^- to Br^- to Cl^-, the relative effectiveness of DMSO-d_6 also increases in this order.

Asymmetric *p*-benzynes, like **4**, show little selectivity between the two sites. This explains the 1:1 ratio of sporolides A/B or of cyanosporasides A/B.[3] Low selectivity also explains incorporation of Br^- from seawater. In contrast, reaction with H_2O is calculated to be endothermic, so it is unlikely to compete. This unreactivity also raises the possibility that reaction of the *p*-benzyne with nucleophiles is another mechanism besides atom abstraction for detoxifying enediyne antibiotics.[28]

This mechanism can account for the biosynthesis of sporolides and cyanosporasides. Moreover, it accounts for their isolation as 1:1 mixtures and for their single chlorines. Scheme 3 thus provides a pathway for attaching X^- to an unactivated aromatic ring. It is consistent with the kinetic data that show that the rate of the reaction is first order in enediyne and independent of the concentrations of acid and halide and even independent of which halide is present. The remarkable result is that this reaction represents a new method for halogenation in both nature and the chemical laboratory. Experiments are underway to explore the extension to other enediynes and to azaenediynes and enyne-allenes,[29] as well as to other nucleophiles and electrophiles. We anticipate that this reaction is a general one for incorporating nucleophiles into aromatics.

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Supporting Information Available: Figure S1, thermodynamic values for Table 2 and their sources, complete ref 11, calculated energies for Table 2 and Cartesian coordinates of structures, Figure S2. This material is available free of charge via the Internet at http://pubs.acs.org.

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