Mini Review

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Reactivity of nucleophiles toward a *p*-benzyne derived from an enediyne†

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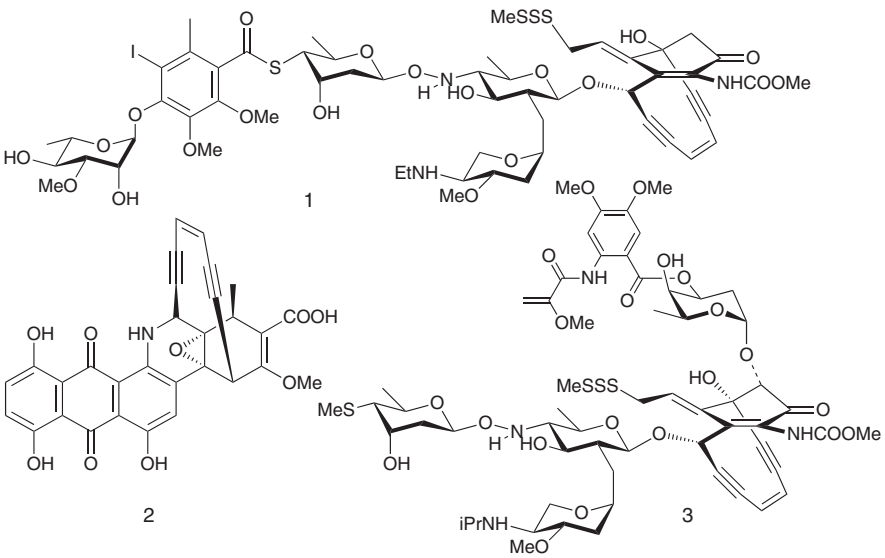
Enediynes undergo cycloaromatization to *p*-benzyne diradicals. A new reaction of *p*-benzynes is here presented. Instead of their usual radical reactivity, they add nucleophiles, followed by protonation. Kinetic evidence showed that the rate-limiting step is the cycloaromatization, followed by rapid addition of a nucleophile. The unusual feature of nucleophilic addition to a radical center in a singlet diradical is discussed. Calculations that ignore solvation suggest that the addition has no activation barrier, but one is created by the necessity for desolvation of the anionic nucleophile. Relative reactivities of several nucleophiles have been measured under competition conditions. The observation of deuterium incorporation from DMSO-d_6 or CD_3CN shows that the species that is protonated is the aryl anion, not the *p*-benzyne. The extent of deuterium incorporation increases as the nucleophile is changed from iodide to bromide to chloride. This remarkable instance of selectivity is discussed. These studies of *p*-benzyne reactivity are exploring the nonradical chemistry of this diradical. Copyright © 2012 John Wiley & Sons, Ltd.

Keywords: enediyne; cycloaromatization; *p*-benzyne; diradical; nucleophilic addition; selectivity; solvation

INTRODUCTION

Enediynes are fascinating substances, with relevance to biosynthesis and with important bioactivity. Enediynes such as calicheamicin γ_1 (**1**), dynemicin A (**2**), and esperamicin A_1 (**3**) have aroused much interest because of their antibiotic activity and toxicity.[1] They act by cycloaromatizing to a *p*-benzyne diradical, followed by abstraction of hydrogen atoms from DNA, leading to double-strand cleavage.



The behavior of *p*-arynes has been studied extensively.[2] They react by atom abstraction, consistent with their diradical character. For example, the parent *p*-benzyne, formed reversibly by cyclization (Bergman rearrangement) of cis-hexa-1,5-diyn-3-ene, can abstract hydrogen atoms from organic molecules such as 1,4-cyclohexadiene or chlorine atoms from CCl_4 (Scheme 1).[3] We became interested in this topic through our colleagues' discovery of the chlorine-containing natural products cyanosporasides A and B (**4a**,**4b**, R = 3-oxo-4-methyl-β-fucosyl) and sporolides A and B (**5a**,**5b**), isolated from marine actinomycete bacteria.[4] In both cases, the two regioisomers A and B differ simply by interchanging the positions of H and Cl. Biosynthetic pathways suggested that the precursor to these substances is a nine-membered-ring enediyne that cyclizes to a *p*-benzyne, as shown in Scheme 2 for **4a**,**4b**.[5] Because abstraction of exactly

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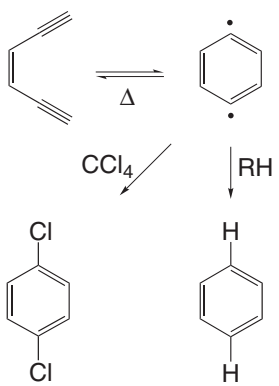
Biography

Born in Pittsburgh in 1938, Charles L. Perrin graduated from Harvard College in 1959 and received his Ph.D. in 1963 from Harvard University, under the direction of the late F. H. Westheimer. Following an NSF Postdoctoral Fellowship at UC Berkeley, he joined the founders of the new campus at UC San Diego, where he is now Distinguished Professor of Chemistry (not emeritus). He has held visiting professorships in Göteborg, Paris, Padua, and Copenhagen, and he has won numerous UCSD teaching prizes. His research spans a broad range of structural and mechanistic chemistry, including anomeric effects, stereoelectronic control, isotope effects, dynamic NMR, solvation, hydrogen bonding, and p-benzyne diradicals. He is currently the chair of a task force to update the IUPAC Glossary of Physical Organic Chemistry. His outside interests include travel, gardening, food, puzzles, and tennis.

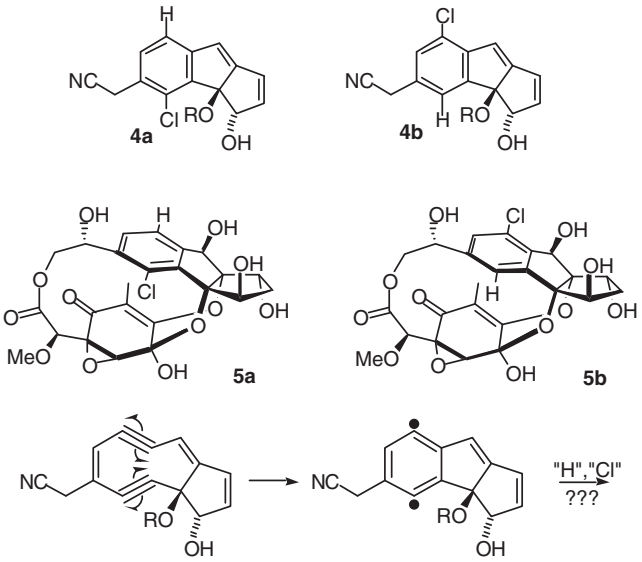
Biography

Originally from the city of Bayamón, Gabriel J. Reyes-Rodríguez received his B.S. in Chemistry in 2008 from Universidad de Puerto Rico, Río Piedras, and received the 2008 *Isidoro Alberto Colón Medal* for the Outstanding Student in Chemistry. There he did research under the supervision of Dr. Olga L. Mayol-Bracero into the chemical composition of clouds and rainwater, and how this composition would change with different air masses arriving to the main island. Currently he is pursuing his Ph.D. at the University of California, San Diego under the direction of Charles L. Perrin. His research includes exploring the reactivity of *para*-benzyne intermediates derived from enediynes and their unusual reactivity towards anionic nucleophiles. Also, he serves as a teaching assistant in organic chemistry courses. His outside interests include music, sports, and orchids.

one hydrogen and one chlorine by that *p*-benzyne seemed unlikely, the question arose as to whether the source of the chlorine in these marine natural products might be chloride from sea water.[6]

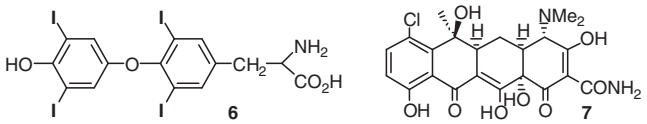


Scheme 1. Formation and capture of *p*-benzyne



Scheme 2. Partial biosynthetic pathway to cyanosporasides (**4a**,**4b**)

Haloaromatics are widespread in the biosphere. Among the most familiar are the thyroid hormone thyroxine (**6**) and the antibiotic chlortetracycline (**7**) from *Streptomyces*. The biosynthesis of such haloaromatics requires a halogenase or a haloperoxidase to oxidize a halogen to an electrophile capable of substituting on an aromatic ring.[7] Incorporation of halogen as halide anion would be a different pathway.



A NOVEL MECHANISTIC POSSIBILITY

Addition of chloride or other nucleophile to a *p*-benzyne had never been proposed, although there are analogies, among which the best known are the additions to the triple bond of *o*-benzynes.[8] Other examples are gas-phase additions to cationic *m*- and *p*-benzynes, which often occur only in the reverse direction,[9–11] and the addition of alcohol to 9,10-dehydroanthracene, which was proposed to occur via opening to a benzotrienediyne,[12] perhaps because *p*-benzyne abstracts a hydrogen atom from methanol, rather than adding methanol as a nucleophile.[3]

The closest analogy to halide addition to a *p*-benzyne is the $S_{RN}1$ reaction,[13] where a nucleophile Nu^- adds to an aryl radical Ar·, to form the radical anion $ArNu^{\cdot-}$. The reaction requires strong nucleophiles, like NH_2^-. For weaker nucleophiles, such as halide X^-, the addition to Ar· is unfavorable thermodynamically. Instead, the favorable reaction is for the unstable $ArX^{\cdot-}$ to dissociate to $Ar\cdot + X^-$. The combination of these two steps then establishes a chain reaction that, once initiated, converts ArX to ArNu. The instability of $ArX^{\cdot-}$ would suggest that addition of X^- to a *p*-benzyne would also be unfavorable thermodynamically. Besides, a *p*-benzyne diradical is generally even less reactive than an aryl radical because of orbital interactions that stabilize the diradical.[14] However, the analogy is imperfect, because the unpaired electron of $ArX^{\cdot-}$ is antibonding, in a π^* or σ^* orbital,

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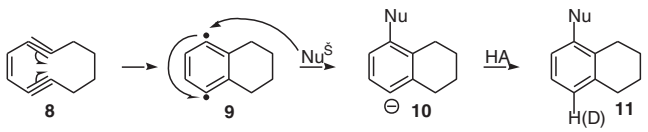
whereas addition of X^- to a *p*-benzyne would create an anion with all electrons paired in σ orbitals. Indeed, there were thermodynamic data available to support halide addition to a *p*-benzyne, sufficient to encourage us to pursue this.

EXPERIMENTAL TEST

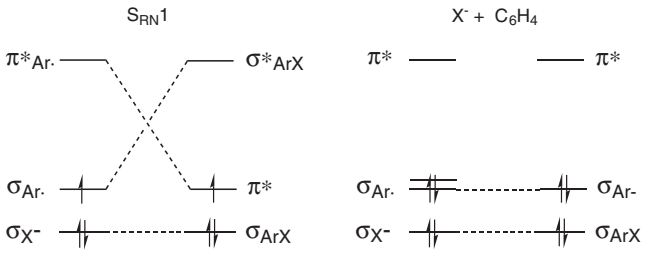
To test the possibility of halide-ion addition to a *p*-benzyne, we studied the kinetics of the conversion of cyclodeca-1,5-diyn-3-ene (**8**) to 1-halotetralin (**11**) in DMSO-d_6 in the presence of lithium halide and added carboxylic acid RCOOH (to provide a proton source, as needed to balance the chemical equation).[15] The product of the reaction is indeed the halotetralin (**11**), according to both ^{1}H NMR and GC-MS. Disappearance of the vinyl signal of **8** and appearance of the aromatic signals of **11** are easily followed by ^{1}H NMR. The kinetics are simply first order in **8**, with a rate constant of $(1.38 \pm 0.12) \times 10^{-5}$ s^{-1} at 37 °C. What is more revealing is that the kinetics are zero order in both halide and acid. The rate is even independent of whether the halide is chloride, bromide, or iodide. Therefore reaction proceeds via rate-limiting electrocyclization of the enediyne to a para-benzyne (**9**), which rapidly adds nucleophile to produce an aryl anion (**10**), which is then protonated, even by a weak acid. This is the same reasoning as was applied to the rates of cycloaromatization of a bicyclic enediynone and a bicyclic enediynol, which are independent of the concentration of hydrogen-atom donors.[16]



This nucleophilic addition contrasts with the usual reactivity of a diradical, which proceeds via atom abstraction. An unusual feature in the reaction of **9** is the combination of a two-headed arrow, pushing two electrons, and a single-headed arrow, pushing one electron. Alternatively, because the diradical (**9**) is born as the more stable singlet,[17] the two "unpaired" electrons are paired and can be considered as forming a C–C bond across the ring. The bond is actually an antibond, with a node between the two atomic orbitals, as in **12**, owing to stabilizing interactions of the HOMO with other σ orbitals.[18] Then the nucleophilic addition becomes an S_N2 reaction (**13**), with the opposite carbon as leaving group. Regardless of how the pathway is rationalized, this represents a new reaction.

COMPUTATIONS

Scheme 3 compares the orbital-correlation diagrams for the $S_{RN}1$ reaction and the proposed nucleophilic addition to a diradical. For $S_{RN}1$, electron transfer from σ to π* does not conserve orbital symmetry but proceeds along a dotted diagonal to σ*. Consequently an energy barrier is created (although in some cases, with



Scheme 3. Orbital-correlation diagrams for Ar· + X^- and for *p*-benzyne + X^-

electronegative X, the σ* orbital lies below the π*).[19] In contrast, no symmetry barrier arises in the addition of a nucleophile to a *p*-benzyne diradical because the HOMO of the reactant, although antibonding between the carbon centers, as in **12**, is σ, and proceeds along the horizontal dotted line to the σ lone pair in the product. Indeed, our UBPW91/6-311 G + (d,p) calculations,[20] with the command Guess = (Mix,Always) to account for the diradical nature,[21] show that the addition of Cl^- to *p*-benzyne is exothermic by 37 kcal/mol, and with no barrier. Figure 1a shows the calculated energy diagram for this addition. Of course, this is a gas-phase calculation that ignores solvation and thus overestimates the exothermicity. Indeed, our UBPW91/6-31 + G(d) calculations, with the polarizable continuum model for simulating the solvent effect of DMSO, shows an exothermicity of only 18 kcal/mol and with a barrier of ~5 kcal/mol, as shown in Fig. 1b. As a further example of the importance of ionic solvation, the gas-phase addition of neutral NH_3 to *p*-benzyne is calculated to be exothermic by only 6 kcal/mol, with a 6 kcal/mol barrier.

The absence of a barrier, other than that due to solvation, in addition of halide to a *p*-benzyne accounts for the lack of regioselectivity in the formation of cyanosporacides A and B and sporolides A and B. Addition to either carbon of the diradical is equally likely. However, a barrier-free reaction would be encounter controlled, and all nucleophiles would react at the same rate. In experiments with a single nucleophile, all nucleophiles do react at the same rate, because the rate-limiting step is the cyclization of the enediyne to the *p*-benzyne. However, in experiments where two nucleophiles compete for the *p*-benzyne intermediate, different nucleophiles react at different rates. The apparent absence of an energy barrier in Fig. 1a is an artifact due to calculations that ignore solvation. To react, a nucleophile must undergo desolvation, which introduces an energy barrier, as suggested in Fig. 1b. As a result, the more strongly solvated

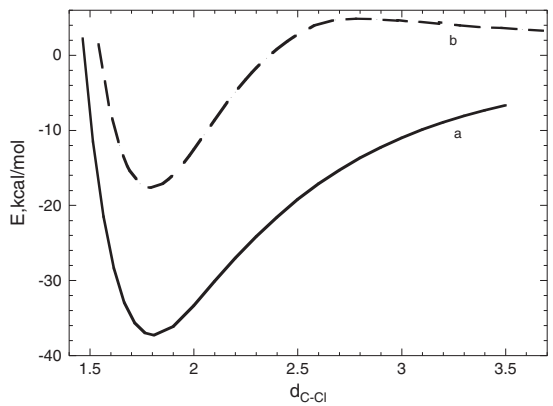


Figure 1. Calculated energy diagrams for reaction of Cl^- with *p*-benzyne: (a) UBPW91/6-311G+(d,p) gas-phase. (b) UBPW91/6-31+G(d) in DMSO

Table 1. Relative reactivities of nucleophiles toward **9**

Nu	I	SCN	Br	N_3	CN	OAc
I		92:8	96:4	>95:5	>95:5	100:0
SCN	8:92		65:35	40:60	-------	100:0
SCN(X10)	50:50		-------	-------	-------	-------
Br	4:96	35:65		50:50	70:30	100:0
N_3(X10)	33:67	-------	-------		-------	-------
CN(X10)	23:77	-------	90:10	-------		-------
Cl	-------	-------	5:95	-------	-------	-------
OAc(X10)	-------	-------	10:90	-------	-------	

nucleophiles react more slowly, and less well-solvated nucleophiles compete more effectively for the *p*-benzyne.

RESULTS

We have therefore extended the kinetic studies to the generation of *p*-benzyne **9** in the presence of an excess of a variety of nucleophiles. The reaction succeeds with other nucleophiles, including cyanide, thiocyanate, azide, and acetate. Products were characterized by GC-MS and ^{1}H NMR. Also, according to infrared analysis, thiocyanate reacts at sulfur, even though ArN=C=S is the more stable isomer.[22] Relative reactivities were measured by assaying the product ratio by GC or NMR. For example, in DMSO, iodide is more reactive than bromide, bromide is ca. 20 times as reactive as chloride, and hydrogen-atom abstraction from 1,4-cyclohexadiene proceeds 2.5 times as rapidly as Br^- adds to **9**.[15]

Table 1 lists relative reactivities of nucleophiles toward the *p*-benzyne diradical **9**, from product ratios as measured by GC. These are preliminary values, awaiting more accurate data from NMR or GC with FID detection. From such studies, the order of reactivity toward **9** is $I^- > NCS^- > Br^- \sim N_3^- \geq NC^- > Cl^- > AcO^-$. This is not an intrinsic reactivity scale of these nucleophiles. Instead, it reflects their ease of desolvation, with the smaller, more highly solvated ions being slower.

Deuterium can be incorporated from DMSO-d_6 or CD_3CN, in competition with the added RCOOH. This observation shows that the species that is protonated is the aryl anion, not the insufficiently basic *p*-benzyne. This result removes a mechanistic ambiguity by eliminating the alternative in which protonation precedes nucleophilic addition, which would be equally consistent with the kinetics. The observation that DMSO can compete with RCOOH as a proton donor, despite a difference in pK_as of 22.5,[23,24] is testimony to the high basicity and unselectivity of the aryl anion. Of course, the solvent is in large excess, and hydrogen bonding of the RCOOH to the DMSO may retard protonation by RCOOH.

The extent of deuterium incorporation from DMSO-d_6, shown in Table 2, increases as the nucleophile is changed from iodide to bromide to chloride.[15] This remarkable selectivity is too large to arise from a substituent effect of the remote halogen on the basicity of the anion. Instead, it is attributed to solvation of the halide by the RCOOH. The smallest ion, Cl^-, is most tightly solvated, thereby rendering RCOOH less reactive as a proton donor.

Table 2. % Deuterium incorporation into 1-halotetrahydronaphthalene (**11**)[15]

X	NMR	GCMS
Cl	67	60
Br	51	44
I	42	40

SUMMARY AND OUTLOOK

A new reaction of *p*-benzynes has been presented. Instead of the usual radical reactivity of these diradicals, they add nucleophiles, followed by protonation. Although calculations which ignore solvation suggest that the addition has no activation barrier, a barrier is created by the necessity for desolvation of the nucleophile. Relative reactivities of several nucleophiles have been measured, along with the relative kinetic acidities of RCOOH and DMSO toward the aryl anion.

Further studies will address additional nucleophiles, including fluoride (for which we have so far had no success), synthetically more useful ones, such as $(EtOCO)_2CH^-$, and a dialkyl phosphate, to test for protection of DNA against double-strand cleavage. The kinetic isotope effect on the protonation of the aryl anion can be measured by assaying the deuterium content of the product. We will explore alternatives to protonation for the capture of the aryl anion by electrophiles such as I_2, CH_3I, acetic anhydride, and $(CH_3)_3SiCN$. Asymmetric enediynes will test whether substituent effects in the *p*-benzyne can affect the regiochemistry, although this is a synthetic challenge. Such studies will define the nonradical chemistry of this diradical.

Acknowledgments

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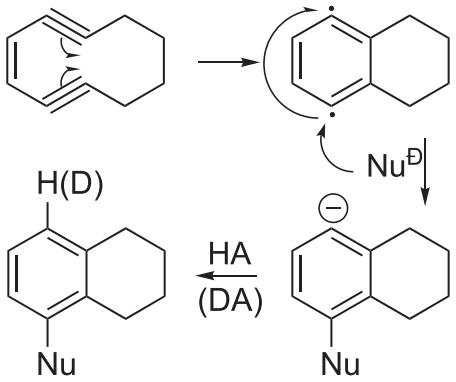

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