9,10-Dehydroanthracene: *p*-Benzyne-Type Biradicals Abstract Hydrogen Unusually Slowly

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Received January 19, 1996[⊗]

Abstract: The 9,10-dehydroanthracene biradical, a model for the *p*-benzyne-type biradicals implicated in DNA cleavage by the enediyne antitumor antibiotics, was prepared by photodissociation of a propellane in solution. Trapping products characteristic of biradicals, e.g. anthracene-d_2, are found. The rates of hydrogen abstraction by the biradical from acetonitrile and isopropyl alcohol are measured directly by flash photolysis/transient absorption spectroscopy, giving second-order rate constants of $k_{\mathrm{MeCN,abstr}} = (1.1 \pm 0.2) \times 10^3\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$ and $k_{i\text{-PrOH,abstr}} = (6.5 \pm 0.6) \times 10^3\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$ at room temperature, which are 100−200 times lower than the corresponding rate constants for phenyl or 9-anthryl radical. A second decay route for the biradical is found, and assigned, based on thermochemical, kinetic, and trapping arguments, to a retro-Bergman reaction that converts the 9,10-dehydroanthracene biradical into the ring-opened 3,4-benzocyclodeca-3,7,9-triene-1,5-diyne. Although the retro-Bergman reaction is relatively fast, $k \approx 4 \times 10^5\ \mathrm{s}^{-1}$ at room temperature, it is competitive with hydrogen abstraction by the biradical only because the hydrogen abstraction is slower than expected. Through-bond coupling in the 1,4-biradical is discussed as a rationalization for the 100- to 200-fold reduction in the abstraction rate.

Introduction

The chemistry of 1,4-biradicals structurally related to *p*-benzyne has recently become the target of renewed activity, following the realization that these biradicals are the likely intermediates in the biological activity of the enediyne group of antitumor antibiotics[1] exemplified by calicheamicin, dynemicin, and esperamicin. In prior studies, the substituted *p*-benzyne biradicals were generated by pericyclic closure of cyclic enediynes,[2] subsequent to a chemical triggering event, to afford a trappable species. The process of biradical formation has been thoroughly explored, with both strain energy[3] and spatial proximity[4] of one terminus of the enediyne system to the other as indices to which cyclization rate can be correlated. Nevertheless, it has been commented upon that neither criterion alone provides a satisfactory explanation of all of the extent data.[5] In further studies, benzannelation of the enediyne has been reported variously to have either no effect[5] or a marked decelerating effect[6] on the Bergman cyclization. Moreover, experimental evidence for a kinetically-significant reversibility of the Bergman cyclization in at least some cyclic systems has recently emerged.[6,7]

Another issue important to the modification and rational design of biradical-based therapeutic agents has remained wholly unexplored though, despite the intense activity in this area. Because thermal cyclization of the enediyne has itself been rate limiting in most of the mechanistic studies, there have been no kinetic data pertaining to the subsequent chemistry of the biradical. In particular, the rates of hydrogen atom abstraction are not known, and have been commonly assumed to be the same as those for the comparably substituted phenyl radicals. The hydrogen abstraction rate gains added importance in light of the proposed reversibility of the Bergman cyclization, which would necessarily occur in kinetic competition with ring-opening of the biradical. Motivated by the desire to prepare a *p*-benzyne-like biradical by a fast photodissociation, so that subsequent biradical kinetics could be observed, we have explored the chemistry of **2**. The route **2** → **1** has the additional attractive features of (i) a good UV chromophore in **2** for photodissociation, (ii) easy synthesis from readily available starting materials, (iii) facile modification with either σ or π substituents at sites sterically remote from the reactive centers, and (iv) a good UV chromophore in **1** for transient absorption spectroscopy. There are two previous reports pertaining to **1**. Chapman *et al.*[8] reported the photochemical double decarbonylation of anthraquinodiketene, as a precursor to **1**, from which an anthracene-like absorption spectrum (in a low-temperature glass) and hydrogen and chlorine atom abstractions by the biradical were seen. Neither rate data nor a mass balance were reported in that work. Darby *et al.*[9] reported anthracene in an attempted preparation of 3,4-benzocyclodeca-3,7,9-triene-1,5-diyne (**3**), presumably via the intermediacy of **1**, as indicated by deuterium incorporation at the 9,10 positions. As in the previous work, no mass balance or rates were reported.

We report here the successful determination of absolute rates, both for the hydrogen abstraction reaction of **1** from acetonitrile and isopropyl alcohol, and for a competing kinetic process, which we attribute to a retro-Bergman reaction in solution. We find that, in agreement with qualitative valence bond considerations and *ab initio* calculations[10] at the CASPT2N level, hydrogen abstraction by **1** is up to 100−200 times slower than

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[⊗] Abstract published in *Advance ACS Abstracts,* May 1, 1996.

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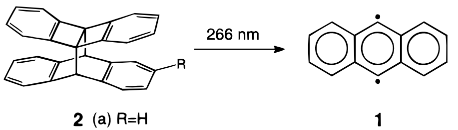
S0002-7863(96)00181-3 CCC: $12.00

Scheme 1



2 (a) R=H
(b) R=CH_3

1

that for the comparable monoradical (9-anthryl or phenyl in this case). Furthermore, we find that the competing process, assigned as ring-opening of **1** to 3,4-benzocyclodeca-3,7,9-triene-1,5-diyne (**3**), is also fast, with a rate of $k \approx 4 \times 10^5$ s^{-1} at room temperature. A nucleophile-induced transannular cyclization of strained enediynes is suggested as the origin for the ionic trapping products previously attributed to dipolar biradicals.

Experimental Section

The synthetic route to **2** is modified from the procedure by Applequist and Searle.[11] Anthracene (for **2a**) or 2-methylanthracene (for **2b**) and 9,10-dichloroanthracene were co-irradiated (Hanovia 450-W medium pressure Hg lamp/uranyl glass filter) in degassed CH_2Cl_2 solution to afford the $4\pi_s + 4\pi_s$ adduct in moderate yield (63% for anthracene and 50% for 2-methylanthracene after column chromatography on silica gel). Reduction of the anthracene−dichloroanthracene adduct with triphenylmethyl sodium and subsequent recrystallization of the product from superheated ether yields analytically pure **2a** in 50% isolated yield as a stable, crystalline solid. **2a**: mp 338−342 °C dec; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS) δ 4.96 (s, 2H), 6.89 (m, 8H), 7.02 (dd, 4H), 7.14 (dd, 4H); MS (70 eV EI), *m/z* 354 (100) M$^+$; UV/vis (MeCN) λ_{max} (ϵ) 283 (3818), 274 (5127), 269 (5194), 215 (60000). The analogous reduction of the 2-methylanthracene−dichloroanthracene adduct proceeds in much lower yield, with the consequence that the **2b** does not crystallize from the reaction mixture without an intermediate purification by column chromatography on silica gel. Subsequent recrystallization from xylene affords **2b** in 10% yield with >99.5% purity, as judged by NMR and GC/MS. Curiously, the only detectable impurity is the known anthracene photodimer, which was not present in the mixture prior to chromatography. **2b**: mp 253−255 °C dec; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, TMS) δ 2.15 (s, 3H), 4.92 (s, 1H), 4.93 (s, 1H), 6.71 (m, 1H), 6.91 (m, 6H), 6.99 (s, 1H), 7.04 (m, 5H), 7.14 (m, 2H); MS (70 eV EI), *m/z* 368 (100) M$^+$; UV/vis (MeCN) λ_{max} (ϵ) 280 (4200), 273 (5810), 215 (49600). Anal. Calcd for $C_{29}H_{20}$: C (94.53); H (5.47). Found: C (94.30); H (5.58).

Bulk irradiation was done on degassed, 100 μM solutions of **2** at 266 nm (Spectra-Physics GCR-3G Nd^{3+}-YAG, 6-ns pulse width, 20 Hz unfocused, 100 mW average power) in a vigorously stirred, long-path cell set so that all of the incident UV laser light is absorbed. Workup consisted of only filtration of the photolysate through a short plug of silica gel to remove insoluble material resulting from the photoreaction, followed by careful evaporation of solvent under reduced pressure. Laser power measurements for quantum yield determination were made with a Scientech (Arapahoe, CO) Model 390107 calibrated laser pyrometer. The frequency-quadrupled YAG laser was used instead of a more conventional light source because of the particular constraints posed by **2**. There exists a narrow spectral window around 270 nm in the absorption spectrum of anthracene or 2-methylanthracene in which the arene itself would not be an internal filter. Fortunately, **2** has an absorption maximum near this window; at 266 nm, ϵ for **2a** and anthracene are 4560 and ~200, respectively, so electronic excitation of anthracene or 2-methylanthracene (especially at low conversions of **2** to products) can be ignored. Fluorescence quantum yields were measured against naphthalene as a standard in a Perkin-Elmer LS-50B luminescence spectrometer and are uncorrected. GC/MS measurements were performed in EI mode on a Fisons MD800 instrument equipped with a DB-5 capillary column. Relative detection sensitivity for **2**, anthracene, and 2-methylanthracene in the GC/MS was determined directly by injection of reference solutions containing equimolar amounts of the analytes. The derived sensitivity factors were used to convert integrated peak areas into true product ratios. For the 9-methoxyanthracene and 9-ethoxyanthracene versus anthracene or 2-methylanthracene, the GC/MS peak areas were calibrated against ^{1}H NMR integrations. Because of the trace, <0.5%, contamination of **2b** by anthracene photodimer, a small correction is included in the reported product ratios. Ordinarily, the effect would be negligible for such a small impurity, but the relative quantum yields for photodissociation of anthracene photodimer ($\phi = 0.55$)[12] versus **2b** ($\phi = 0.01$) mean that roughly 10% of the detected anthracene from samples of **2b** derives from the impurity. While the anthracene/2-methylanthracene ratio over several GC/MS injections of a single sample is reproducible to within 1%, the run-to-run variability of the ratio in identically treated samples is about 10%.

Flash photolysis experiments were performed at room temperature with an Applied Photophysics (Leatherhead, Surrey, U.K.) laser kinetic spectrometer, adapted to operate with a Spectra-Physics GCR-3G Nd^{3+}-YAG laser. Transient absorption spectra with lifetimes in the range from 10 ns to >500 μs, with OD changes of at least 5×10^{-4}, can be observed cleanly following laser photolysis at 266 nm (10 mJ/pulse). The degassed solution, typically 80 μM concentration, was flowed through a well-stirred quartz cuvette at a rate sufficient so that all products from one laser shot are flushed away before the next shot. Removal of the product arenes from each shot prior to the next was found to be crucial in that both the anthracenes and their metastable triplets have broad, intense UV/vis absorption spectra that mask the spectral regions in which we needed to work. The role of diffusion out of the observation zone for transient decays up to the millisecond time scale could be excluded by tracking the temporal profile of the 251-nm anthracene band ($\epsilon = 220\,000$) following a single laser shot. The single-shot conversion could also be determined from the absorption at 251 nm to be 0.4% of the material in the irradiated volume. Transient absorption spectra, taken pointwise, were signal averaged over 20 shots at each wavelength to improve the signal-to-noise ratio. Each decay rate is the average of approximately 15 repeated measurements. Uncertainty bounds (1 σ) of about 10% were found for the decay rates, measured on a given run. Repeated runs to determine run-to-run reproducibility gave a comparable uncertainty bound.

All solvents were spectroscopic grade and were checked by UV/vis to ensure that there was no absorbing species at 266 nm.

Ab initio calculations were performed on an IBM RS/6000 Model 590 workstation using the Gaussian 92 and MOLCAS-3 suites of programs.[13] Given the biradical character of the species involved, we judged it essential to use multideterminantal methods to obtain chemically reliable results.[14] Geometries were optimized at CASSCF-(2×2), (4×4), and (6×6) levels with a relatively small basis set, 3-21G. The energies were subsequently recomputed, at the 3-21G geometries, with a much larger basis set, 6-31G*, and perturbative inclusion of dynamic correlation effects. These latter CASPT2N/6-31G* calculations were done with the same (2×2), (4×4), and (6×6) active spaces. The (2×2) active space included only the two nonbonding orbitals of **1**. Adding one pair of σ and σ^* orbitals involved in the through-bond coupling[15] produced the (4×4) active space. Inclusion of two σ and σ^* pairs yielded the (6×6) active space. A full description of the *ab initio* calculations on **1** and its isomers will be given in a subsequent

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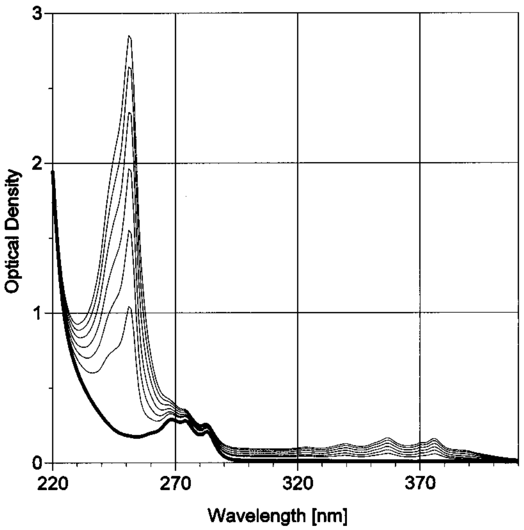

Figure 1. UV/vis absorption spectra for **2a** in acetonitrile. The extinction coefficient of **2a** at 266 nm is 4560. See text for ϵ at other wavelengths. Successive spectra, taken at 30-s intervals during 266-nm photolysis, are overlaid, showing the growth of the anthracene spectrum. The anthracene band systems at 251 ($\epsilon = 220\,000$) and 375 nm ($\epsilon = 7400$) would absorb incident broadband UV, necessitating the use of monochromatic laser photolysis at 266 nm.

publication, along with details of the potential surface for interconversion between isomers.

Results

In the typical bulk photolysis experiment, irradiation of a degassed 100 μM solution of **2a** in acetonitrile at 266 nm affords after 30 min 25% conversion of **2a** to anthracene, as judged by UV/vis spectra taken at regular intervals. The quantum yield of anthracene production is relatively low: $\phi = 0.02$ and 0.01 from **2a** and **2b**, respectively. There is also a surprisingly large fluorescence quantum yield of 0.13 in xylene-like emission peaked at 297 nm (structureless with a fwhm of 26 nm) from **2a**. The absorption spectrum of **2a** prior to photolysis, and at 30-s intervals during photolysis, is shown in Figure 1. The integrated UV absorption cross section of **2a** together with the fluorescence quantum yield yields an excited state lifetime[16] for S_1 of ~1 ns. Given the typical arene intersystem crossing rates[17] of $k_{ST} \sim 10^6 - 10^7$ s^{-1}, it is unlikely that intersystem crossing from the initially-produced S_1 state occurs to a significant extent. The photolyses in acetonitrile produced, in addition to the arenes, an uncharacterizable polymeric material which imparted a visible turbidity and yellow tint to the solution. Photolysis of either **2a** or **2b** in aliphatic alcohols was much cleaner with no visible turbidity or color change. By both ^{1}H NMR and GC/MS analysis, the only products (other than unreacted **2**) after workup at low-to-moderate conversions in the reaction in alcohols were substituted anthracenes. Photoreduction of the anthracene products by the alcohols was evident only at high conversions. In any of the solvents, anthraquinone was formed in large amounts if the solution was not carefully degassed, so care was taken to exclude O_2 from the reaction mixtures. Identification of the products in the irradiations in methanol, ethanol, and isopropyl alcohol was done principally by GC/MS. This was necessitated by the experiments in deuterated solvents, for which a 100 μM concentration of **2** in 10 mL of solvent, run to 25% conversion, meant that there were approximately 0.1 mg of products. The irradiation of **2a** in ethanol was repeated on a 50-fold larger scale to produce enough 9-ethoxyanthracene so that the ^{1}H NMR spectra could be taken to confirm that there was indeed only the ether and none of the isomeric hydroxyethylanthracene. Irradiation of **2a** in CH_3OD yielded, in addition to anthracene, an adduct with the mass spectral fragmentation pattern consistent with 10-methoxyanthracene-*9-d*. The location of the deuterium in the product was confirmed by ^{2}H NMR to be exclusively the 9-position. These experiments are important in that they connect the mass spectra[18] to structures unambiguously determined by NMR. The trapping products for all of the other experiments in alcohols could then be identified with confidence by GC/MS alone. A representative total ion GC/MS trace for the products of bulk photolysis is shown in Figure 2 to illustrate the cleanliness of the photoreaction. The results of the trapping experiments are summarized in Table 1. One should note that, in the photolyses of **2b**, the combined amounts of the anthracene and 9-alkoxyanthracene products do not add up to the amount of 2-methylanthracene, even for the photolysis in isopropyl alcohol. In that case, with the best hydrogen-donating solvent[19] used in this study, approximately 65% of the reactive intermediates produced in the photodissociation were captured as isolable products.

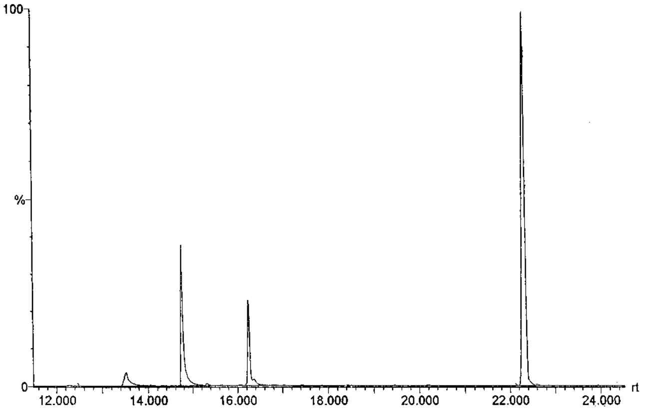

Figure 2. Representative total ion GC/MS trace for the photolysate of **2b** in isopropyl alcohol. The four peaks are identified (with retention times in minutes) as anthracene (13.5), 2-methylanthracene (14.8), 9-isopropoxyanthracene (16.3), and **2b** (22.3) by their 70-eV EI mass spectra.

In the flash photolysis experiment, two transients were observed following photolysis of **2a** at 266 nm. The transient absorption spectra are shown in Figures 3 and 4. The same two spectra were observed in both degassed CH_3CN and isopropyl alcohol, indicating that solvent-derived species were not involved. The decays for both transients were first order[20] and give lifetimes in CH_3CN of $\tau = 2.6$ μs and 1.0 ms. In

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[17] Turro, N. J. *Modern Molecular Photochemistry*; Benjamin/Cummings: Menlo Park, CA, 1978; p 111. Given the similarity of both the absorption and dispersed fluorescence spectra of **2** to those of *o*-xylene, the comparison should be a safe one.

[18] EI mass spectra with fragmentation patterns are also reported in the literature for 9-methoxy- and 9-ethoxyanthracene: Gillis, R. G.; Long, G. J.; Moritz, A. G.; Occolowitz, J. L. *Org. Mass. Spectrosc.* **1968**, *1*, 527. Klasinc, L.; Komadinovic, S.; Stefanovic, D.; Guesten, H. *Croat. Chem. Acta* **1976**, *48*, 109.

[19] The choice of hydrogen donors is limited by the need to photolyze at 266 nm. For example, although 1,4-cyclohexadiene is transparent at the photolysis wavelength, it is unavoidably contaminated with 1,3-cyclohexadiene and benzene, both of which absorb strongly enough at 266 nm to cause problems when they are present at the ~1% level in the solvent. Benzylic donors such as cumene also cannot be used because of their $\pi\pi^*$ transitions in the near-UV.

[20] For the slowest decay, $\tau = 1.0$ ms, the decay could be followed out for <2 lifetimes. Although the decay is first-order as far as we can determine, we do not exclude the possibility that instrumental limitations prevent us from seeing nonexponential behavior in the longest-lived transient. Error bounds were determined on the decay rates rather than on the lifetimes, and are reported with those rate measurements.

Table 1. Product Ratios in the Photolyses of **2a** and **2b** in acetonitrile and aliphatic alcohols, As Determined by Calibrated GC/MS Integrations[a]

trapping agent (solvent)	2a	2b
CH_3CN	An + polymer	An + 2-MeAn + polymer [1:18]
CD_3CN	An + polymer	An-d_2 + 2-MeAn + polymer [1:150]
CH_3CN/H_2O	An + polymer	
CH_3OH	An + MeOAn [3.2:1]	An + 2-MeAn + MeOAn [1:12:6.7]
CH_3OD	An + MeOAn + MeOAn-*d* [8.8:1.7:1]	
CD_3OD		An-d_2 + 2-MeAn + MeOAn-d_4 [1:23:6.9]
CH_3CH_2OH	An + EtOAn[2.3:1]	An + 2-MeAn + EtOAn[1:7.3:5.2]
$(CH_3)_2CHOH$	An + *i*-PrOAn [2.4:1]	An + 2-MeAn + *i*-PrOAn [1:5.7:2.8]
$(CD_3)_2CDOD$		An-d_2 + 2-MeAn + *i*-PrOAn-d_8 [1:10:3.0]

[a] The products and abbrevations are as follows: anthracene (An), 2-methylanthracene (2-MeAn), anthracene-*9,10-d_2* (An-d_2), 9-methoxyanthracene (MeOAn), 10-methoxyanthracene-*9-d* (MeOAn-*d*), 10-perdeuteriomethoxyanthracene-*9-d* (MeOAn-d_4), 9-ethoxyanthracene (EtOAn), 9-isopropoxyanthracene (*i*-PrOAn), 10-perdeuterioisopropoxyanthracene-*9-d* (*i*-PrOAn-d_8). Run-to-run reproducibility of the observed ratios is approximately 10%.

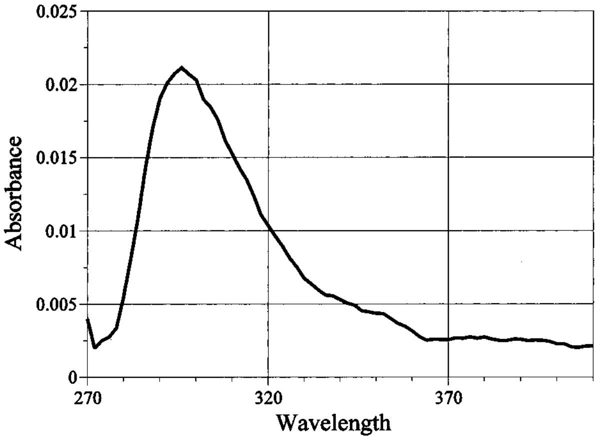


Figure 3. Transient absorption spectrum for the fast transient from photolysis of **2a** in isopropyl alcohol. The spectrum was taken 0.2 μs after the laser shot.

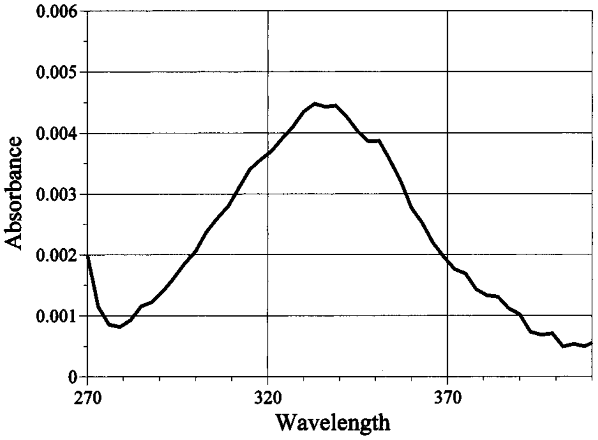


Figure 4. Transient absorption spectrum for the slow transient from photolysis of **2a** in isopropyl alcohol. The spectrum was taken 80 μs after the laser shot to exclude any contribution from the fast transient.

isopropyl alcohol, the corresponding lifetimes were shorter, with $\tau = 2.1$ and 500 μs for the "fast" and "slow" transients, respectively. The spectrum of the slow transient is much weaker than that of the fast transient, presumably due to a lower extinction coefficient, and is partially overlapped by the 375 nm band system of anthracene produced by the same laser shot. Accordingly, the lifetimes were taken at the high-energy side of the band, where anthracene absorption is negligible. The risetime of the fast transient is not detectable on the fastest time scales available to us, and that for the slow transient at short times is obscured by the partially overlapping absorption of the fast transient. The temporal profile at 251 nm shows a large jump in optical density that cannot be resolved within the 10-ns limit of the instrument, followed by a slow increase over time. The rate of the increase is difficult to determine accurately because it is a small increment on top of a large offset, but single exponential fits yielded rate constants for the appearance of anthracene after the initial 10 ns of approximately 2×10^4 and 5×10^4 s^{-1} in acetonitrile and isopropyl alcohol, respectively. The reliability of these latter two values is difficult to assess, but they are certainly good to within a factor of 2.

Relative energies for the three isomers, **1**, **3**, and **4**, along with the key bond lengths and complete geometry specifications in Cartesian coordinates are given in Table 2. The computational results are preliminary in the sense that only the three isomers are reported here. A complete study is underway to compute the potential surface on which the three isomers would interconvert. Nevertheless, for the purpose of facilitating interpretation of the present experimental results, the relative energies of **1**, **3**, and **4** are sufficient.

Discussion

The trapping studies, in particular the observation of anthracene-d_2 from **2b** in perdeuterated methanol and isopropyl alcohol, clearly support the intermediacy of the 9,10-dehydroanthracene biradical **1** in the photochemical reactions of **2** as a qualitative conclusion. A more quantitative look at both the trapping and flash photolysis data produces answers to three important questions: (i) Can the rate of hydrogen abstraction by **1** be extracted from the transient absorption? (ii) One expected to see **1** as a transient in the flash photolysis experiment. What is the second transient? It cannot be 9-anthryl radical, given the known rate of reaction (see below) for that radical. (iii) What is the origin of the 9-alkoxyanthracene products that accompany anthracene formation in the photolyses of **2** in aliphatic alcohols? One would not consider them to be typical radical trapping products. The three questions will be addressed in sequence, followed by a rationalization of the observed behavior on simple theoretical grounds.

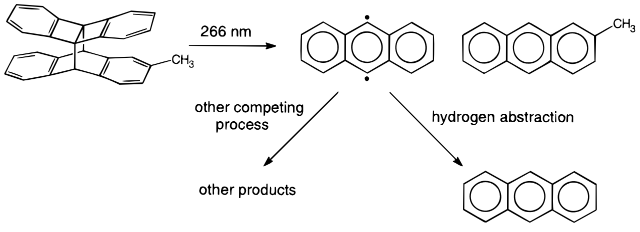
As an answer to the first question, we identify the fast transient in the flash photolysis experiment with the 9,10-dehydroanthracene biradical **1**, which means that the fast transient decay can be related to the hydrogen abstraction rate by **1** from acetonitrile or isopropyl alcohol. One starts with the trapping results for irradiations of **2b** in acetonitrile versus isopropyl alcohol in Table 1. Anthracene clearly derives from hydrogen abstraction from the solvent, and *if there were no other kinetically significant event*, it would be formed in an 1:1 ratio with 2-methylanthracene. Interestingly, the ratio of anthracene to 2-methylanthracene differs markedly from 1:1, going from 1:18 to 1:5.7 as one goes from acetonitrile to isopropyl alcohol. One writes the simple kinetic scheme below, ignoring for the moment the actual identity of the competing process. Using

Table 2. Results of the *ab Initio* Calculations for **1**, **3**, and **4**[a]

1				**3**				**4**			
CAS(6×6)/6-31G*			−534.72002	CAS(6×6)/6-31G*			−534.72937	CAS(6×6)/6-31G*			−534.61089
			0 kcal/mol				−5.9 kcal/mol				+68.6 kcal/mol
CASPT2N/6-31G*			−536.49502	CASPT2N/6-31G*			−536.48897	CASPT2N/6-31G*			−536.41588
			0 kcal/mol				+3.8 kcal/mol				+49.7 kcal/mol
C9−C10			2.70 Å	C1−C2			1.21 Å	C9−C10			1.60 Å
C9−C11			1.37 Å	C2−C3			1.41 Å	C9−C11			1.40 Å
C11−C12			1.47 Å	C3−C4			1.43 Å	C11−C12			1.47 Å
				C2−C5			2.73 Å				
				C1−C6			3.00 Å				
C	0.00000	0.71410	3.63837	C	0.00000	0.69589	3.66474	C	0.00000	3.74724	0.72412
C	0.00000	−0.71410	3.63837	C	0.00000	−0.69589	3.66474	C	0.00000	−3.74724	0.72412
C	0.00000	1.40835	2.48331	C	0.00000	1.39215	2.47787	C	0.00000	3.74724	−0.72412
C	0.00000	−1.40835	2.48331	C	0.00000	−1.39215	2.47787	C	0.00000	−3.74724	−0.72412
C	0.00000	0.73547	1.22206	C	0.00000	0.71416	1.26055	C	0.00000	2.61404	1.46375
C	0.00000	−0.73547	1.22206	C	0.00000	−0.71416	1.26055	C	0.00000	−2.61404	1.46375
C	0.00000	1.35168	0.00000	C	0.00000	1.36380	0.00399	C	0.00000	2.61404	−1.46375
C	0.00000	−1.35168	0.00000	C	0.00000	−1.36380	0.00399	C	0.00000	−2.61404	−1.46375
C	0.00000	−0.73547	−1.22206	C	0.00000	−1.50185	−1.19638	C	0.00000	1.39558	0.73367
C	0.00000	0.73547	−1.22206	C	0.00000	1.50185	−1.19638	C	0.00000	−1.39558	0.73367
C	0.00000	−1.40835	−2.48331	C	0.00000	−1.66854	−2.59428	C	0.00000	1.39558	−0.73367
C	0.00000	1.40835	−2.48331	C	0.00000	1.66854	−2.59428	C	0.00000	−1.39558	−0.73367
C	0.00000	−0.71410	−3.63837	C	0.00000	−0.72660	−3.54863	C	0.00000	0.00000	0.80000
C	0.00000	0.71410	−3.63837	C	0.00000	0.72660	−3.54863	C	0.00000	0.00000	−0.80000
H	0.00000	1.23151	4.57690	H	0.00000	1.22871	4.59438	H	0.00000	4.70170	1.21273
H	0.00000	−1.23151	4.57690	H	0.00000	−1.22871	4.59438	H	0.00000	−4.70170	1.21273
H	0.00000	−2.47962	2.48343	H	0.00000	2.46312	2.47524	H	0.00000	4.70170	−1.21273
H	0.00000	−2.47962	2.48343	H	0.00000	−2.46312	2.47524	H	0.00000	−4.70170	−1.21273
H	0.00000	−2.47962	−2.48343	H	0.00000	−2.69073	−2.92738	H	0.00000	2.63581	2.53442
H	0.00000	2.47982	−2.48343	H	0.00000	2.69073	−2.92738	H	0.00000	−2.63581	2.53442
H	0.00000	−1.23151	−4.57690	H	0.00000	−1.11961	−4.54937	H	0.00000	2.63581	−2.53442
H	0.00000	1.23151	−4.57690	H	0.00000	1.11961	−4.54937	H	0.00000	−2.63581	−2.53442

[A] Total energies (hartress) and relative energies (kcal/mol referenced to **1**) are given for both CASSCF/6-31G* and CASPT2N/6-31G* calculations with the same (6×6) active space. Selected bond lengths and complete Cartesian coordinates (in Å) are given for the geometries optimized at the CASSCF/3-21G level of theory. The geometry optimizations for **1** and **3** were done with a (6×6) active space, while that for **4** was done with a (2×2) active space. The geometry for **4** corresponds to a minimum in the CASPT2N/6-31G* energy, computed at a series of CAS(2×2)/3-21G points describing the **1** → **4** conversion in steps of 0.1 Å in the C9−C10 distance (all other parameters were allowed to relax). The latter contrivance was needed because, although **4** lies in a shallow well according to CASPT2N energies, there is no minimum at the CASSCF level of theory.

Scheme 2



the 2-methylanthracene as an internal reference, and taking the hydrogen abstraction reaction from solvent to be *pseudo* first order, the hydrogen abstraction rates can be derived by a combination of the total decay rate and the product ratios. For CH_3CN and $(CH_3)_2CHOH$ as solvent and hydrogen donor, the lifetimes of the fast transient, $\tau = 2.6$ and 2.1 μs, respectively, correspond to total decay rates of $k_{\mathrm{MeCN,fast}} = (3.8 \pm 0.4) \times 10^5\ \mathrm{s}^{-1}$ and $k_{i\text{-}\mathrm{PrOH,fast}} = (4.8 \pm 0.5) \times 10^5\ \mathrm{s}^{-1}$. Assuming that none of the 2-methylanthracene is removed, the ratio of anthracene to 2-methylanthracene represents that fraction of the total decay rate corresponding to hydrogen abstraction. For CH_3CN and $(CH_3)_2CHOH$, one therefore obtains $(2.1 \pm 0.5) \times 10^4$ and $(8.4 \pm 0.8) \times 10^4\ \mathrm{s}^{-1}$ as *pseudo*-first-order rates of hydrogen abstraction in the two solvents. *The match of these two pseudo-first-order rates, each calculated from a decay of the fast transient combined with a product ratio, to the rate of appearance of anthracene absorption in the same solvent*[21] *confirms that the fast transient is the biradical* ***1***. Using the molarity of neat acetonitrile, 19 M, and isopropyl alcohol, 13 M, the second-order rate constants for hydrogen abstraction by **1** are $k_{\mathrm{MeCN,abstr}} = (1.1 \pm 0.2) \times 10^3\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$ and $k_{i\text{-}\mathrm{PrOH,abstr}} = (6.5 \pm 0.6) \times 10^3\ \mathrm{M}^{-1}\ \mathrm{s}^{-1}$. For the competing kinetic process, which has up-to-now been simply designated as "other", one obtains absolute rates in acetonitrile and isopropyl alcohol by subtracting the *pseudo*-first-order abstraction rates from the total rates. For the reaction in the two solvents, one thus arrives at $k_{\mathrm{MeCN,other}} = (3.6 \pm 0.4) \times 10^5\ \mathrm{s}^{-1}$ and $k_{i\text{-}\mathrm{PrOH,other}} = (4.0 \pm 0.5) \times 10^5\ \mathrm{s}^{-1}$, indicating that, whatever the process is, it has no pronounced solvent dependence. Examining the product ratios for CH_3CN versus CD_3CN and $(CH_3)_2CHOH$ versus $(CD_3)_2CDOD$, one sees that the kinetic isotope effect on hydrogen (deuterium) abstraction is much larger for acetonitrile than for isopropyl alcohol. The variation of k_H/k_D follows the expected trend for hydrogen transfer reactions as a function of the position of the transition state. The kinetic isotope effect is larger for a more symmetrical transition state,[22] which, in this case, means that as the C−H bond strength of the donor approaches that of the arene C−H bond, the isotope effect should increase. The position of the transition state, as measured by the relative rates of H-abstraction, going from acetonitrile to isopropyl alcohol, moves in the proper direction.[23] The deuterium kinetic isotope effect also gives the reason for our

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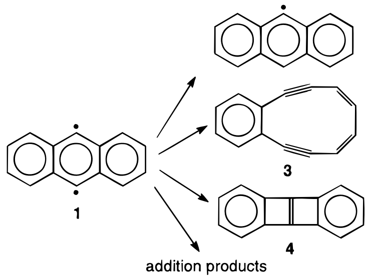
(21) As can be inferred from the identification of the slow transient (see later text), its longer lifetime and much lower ϵ at 251 nm mean that only that fraction of **1** which decays by hydrogen abstraction should contribute to the growth of anthracene absorbance on the microsecond time scale.

(22) Bell, R. P.; Cox, B. G. *J. Chem. Soc. B* **1971**, 783.

Scheme 3



initial trouble in detecting anthracene-d_2 in the photolysis of **2a** in CD_3CN. For acetonitrile, $k_H/k_D \sim 7.5$ and contains a primary plus two secondary deuterium isotope effects for a relatively strong C−H(D) bond. Given that hydrogen abstraction from CH_3CN already barely competes with the "other" kinetic process, deuteration of the solvent would slow the abstraction enough so that anthracene-d_2 would be difficult to detect in the presence of a much larger amount of anthracene produced concurrently in the experiment. One further piece of information can be extracted from the spectrum of the fast transient. By comparison to the anthracene absorption at 251 nm, the molar extinction coefficient of **1** at $\lambda_{max} = 295$ nm can be estimated as $\epsilon \sim 100\,000$.

To answer the second question posed by the results, we propose that the slow transient is the ring-opened structure **3**, 3,4-benzocyclodeca-3,7,9-triene-1,5-diyne. *A priori,* there are three other obvious candidates, the ring-closed butalene[24] isomer **4**, the 9-anthryl radical, and some addition product[25] of **1** and **2** (leading to polymer). We exclude the addition product by a kinetic argument. The concentration of **2** is never above 100 μM, and is often lower. A bimolecular addition reaction with a typical E_a of a few kilocalories per mole would proceed with a *pseudo*-first-order rate of $\sim 10^3$ s^{-1}, which is far too slow to be the process converting **1** to the slow transient. We can also exclude 9-anthryl radical as a candidate for the slow transient on kinetic grounds. The *pseudo*-first-order lifetime of 9-anthryl radical in neat acetonitrile has been reported in an electrochemical study[26] to be only 50 ns, which is much too short to be compatible with the 1.0-ms lifetime of the slow transient in acetonitrile. Because there is no evidence in the flash photolysis experiment that the slow transient reverts to the fast transient up to the millisecond time scale, one infers that the slow transient is a species derived from **1** in an exothermic reaction. With the conditions of the experiment, i.e. room temperature and micro-to-millisecond time scales, the exothermicity of the **1**-to-slow transient reaction need not be more than 2−3 kcal/mol for any reversibility to become kinetically unimportant. Of the remaining two candidates for the slow transient, **3** and **4**, we can now exclude **4** on thermochemical grounds. At the CAS(6×6)/6-31G* level of theory, **4** lies 68.5 kcal/mol above **1**. At the CASPT2N/6-31G* level, the difference falls to 49.7 kcal. It is evident that **4** is much higher in energy than **1**, in contrast to what one infers about the slow transient. It is furthermore thermochemically inaccessible from **2** by photolysis at 266 nm, based on an estimate for ΔH_f[**2a**] starting from the ΔH_f[anthracene] and ΔH for cleavage of anthracene photodimer.[27] The remaining candidate for the slow transient, 3,4-benzocyclodeca-3,7,9-triene-1,5-diyne **3**, is predicted by the CAS(6×6)/6-31G* and CASPT2N/6-31G* calculations to lie 5.9 kcal/mol below and 3.8 kcal/mol above the biradical **1**. At this level of theory, one can only say (conservatively) that *ab initio* calculations place **1** and **3** close in energy. The result is qualitatively reasonable given that the aromaticity of **3** (which is a [10]annulene) would at least partially offset the strain incurred upon inclusion of the acetylenic units within a 10-membered ring. As precedent, a retro-Berman reaction of *p*-benzyne-type biradicals, in competition with hydrogen abstraction, has been recently reported in a model study[7] of the C-1027 chromophore. The experimental evidence, in that case, for kinetically significant reversibility in the Bergman cyclization is unequivocal for the enediyne moiety included in a 9-membered ring. Subsequent reexamination of the literature finds comparable instances in some 10-membered rings as well.[6] Accordingly, it is completely reasonable that **1** could go to **3** in competition with hydrogen abstraction. From the recent redetermination[28] of the Arrhenius parameters for the parent retro-Bergman reaction, *p*-benzyne going to the enediyne, we have $\log A = 14.1$ and $E_a = 20.7$ kcal/mol for the unelaborated biradical. One needs to postulate a reduction of the E_a to approximately 12−13 kcal/mol to bring the retro-Bergman reaction rate of **1** into consistency with $k_{\mathrm{MeCN,other}}$ as determined in an earlier section. The 8 kcal/mol lowering of the transition state for retro-Bergman reaction would imply, by microscopic reversibility (using an estimated 2−3 kcal/mol energy difference between **1** and **3** and the same Arrhenius preexponential factors), that **3**, if it were to be prepared independently, would have a lifetime at room temperature of a few milliseconds with respect to cyclization, making it unisolable under ordinary conditions. Darby *et al.*,[9] in their attempt to produce **3** by a double elimination reaction, recovered only polymeric material and anthracene derivatives, just as the rate estimates imply. With the combination of results from *ab initio* calculation and precedent in other enediyne/radical systems, we make the assignment of the slow transient to 3,4-benzocyclodeca-3,7,9-triene-1,5-diyne (**3**).

Given that we believe the slow transient to be 3,4-benzocyclodeca-3,7,9-triene-1,5-diyne (**3**), the 9-alkoxyanthracene products from photolysis of **2a** or **2b** in aliphatic alcohols must be derived from **3**. The 2-fold reduction of the slow transient's lifetime, from 1.0 ms to 500 μs, going from acetonitrile to isopropyl alcohol, is presumably the kinetic signature of the reaction of **3** with ROH. Trapping of an alcohol on oxygen instead of carbon suggests that the reaction is ionic as opposed to radical-based. Addition of an alcohol across the in-plane π-bond of a strained cycloalkyne is not too surprising. It has been shown experimentally that, while *cis*-bending of an alkyne is accompanied by almost no change in the in-plane π-HOMO energy (as measured by the ionization potential in photoelectron spectroscopy[29]), a marked lowering of the π^*-LUMO occurs (as measured by the electron affinity in electron transmission

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(23) If one uses the *para* C−H bond in phenyl radical as a model, the C−H bond strength in 9-anthryl radical at the 10-position would be 108 kcal/mol, using the $\Delta H_{f,298}$[*p*-benzyne] = 138 kcal/mol as reported independently in two recent works: Wenthold, P. G.; Squires, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 6401; and Reference 28. Because the arene C−H bond is stronger than any of the solvent C−H bonds, one would therefore expect the relative rates for abstraction from acetonitrile and isopropyl alcohol to be a measure of the symmetry of the transition state.

(24) Dewar, M. J. S.; Lee, W.-K. *J. Am. Chem. Soc.* **1974**, *96*, 5569. Breslow, R.; Napierski, J.; Clarke, T. C. *J. Am. Chem. Soc.* **1975**, *97*, 6275. Breslow, R.; Khanna, P. L. *Tetrahedron Lett.* **1977**, 3429.

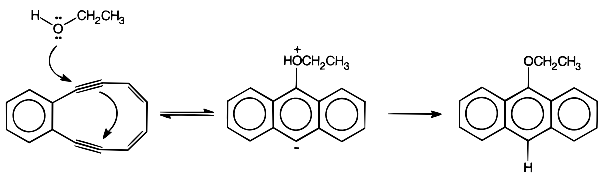
(25) We do not consider addition products of **1** to solvent, e.g. acetonitrile, because the absorption spectrum of the slow transient is unchanged going from acetonitrile to isopropyl alcohol. The next most abundant species in solution to which a radical-like species could add would be unreacted propellane **2**.

(26) M'Halla, F.; Pinson, J.; Savéant, J. M. *J. Am. Chem. Soc.* **1980**, *102*, 4120.

(27) The required ΔH is assumed to be the same as that measured for the photodimer of 9-cyanoanthracene of −20 kcal/mol: Guarini, G.; Sarti-Pantoni, P. *Mol. Cryst. Liq. Cryst.* **1970**, *6*, 423. Dontai, D.; Guarini, G.; Sarti-Pantoni, P. *Mol. Cryst. Liq. Cryst.* **1972**, *17*, 187.

(28) Roth, W. R.; Hopf, H.; Horn, C. *Chem. Ber.* **1994**, *127*, 1765.

Scheme 4



spectroscopy[30]). The same effect appears in computational studies on strained cycloalkynes.[31] Accordingly, strained cycloalkynes ought to be susceptible to attack by nucleophiles. In the case of **3**, nucleophilic attack can induce a transannular cyclization, for which there is ample precedent[32] in the reduction of macrocyclic polyynes. Furthermore, two recent reports[33,34] on macrocycles related to the enediyne series of compounds find transannular cyclization products in which it could be claimed that aromatization is triggered by nucleophilic addition to a strained sp-hybridized site in the ring. Neutral water, a stronger acid and a weaker nucleophile than the alcohols, does not trap **3**. (It would have presumably given anthrone). Products from attack at what becomes the 9-position would be favored if an initial nucleophilic attack were to be reversible. One can speculate that the observation of ionic products in neocarzinostatin and related systems[34] arise not from "dipolar biradicals", i.e. zwitterionic cyclized structures, but rather from nucleophile-induced transannular reactions. Because of the symmetry of both **1** and **3**, there can be no permanent charge separation in the isolated molecules. Although neocarzinostatin itself lacks that symmetry, it would be entirely reasonable that it could react in the same way. It is important to note here that 1,4 σ,π-biradicals such as the α,3-dehydrotoluene biradical studied by Myers *et al.*,[35] in contrast to 1,4 σ,σ-biradicals, probably do react via a dipolar structure[36] made possible by the much greater electronic difference between the two radical sites.

Having suggested answers to the three questions posed at the onset of this section, one should offer a rationale for why the hydrogen abstraction rate for a *p*-benzyne-type biradical should, in fact, be so slow. In the present study, we have measured the second-order rate constants $k_{\text{MeCN,abstr}} = (1.1 \pm 0.2) \times 10^3\ \text{M}^{-1}\ \text{s}^{-1}$ and $k_{i\text{-PrOH,abstr}} = (6.5 \pm 0.6) \times 10^3\ \text{M}^{-1}\ \text{s}^{-1}$. By way of comparison, the analogous second-order rate constants for phenyl radical[37] are $(1.04 \pm 0.18) \times 10^5$ and $(1.38 \pm 0.07) \times 10^6\ \text{M}^{-1}\ \text{s}^{-1}$ for acetonitrile and isopropyl alcohol. The one report of an absolute rate constant for hydrogen abstraction by 9-anthryl radical,[26] which one might argue is more sterically hindered than phenyl, lists $\sim 10^6\ \text{M}^{-1}\ \text{s}^{-1}$ for abstraction from CH_3CN; clearly, any steric difference between phenyl and 9-anthryl radicals is kinetically unimportant. Accordingly, the lowering of the hydrogen abstraction rate for **1** by two orders of magnitude does not derive from steric problems, which leaves electronic factors as the most likely cause. In a recent publication,[10] we have investigated the hydrogen abstraction reactions of *p*-benzyne and phenyl radical from methanol by *ab initio* theory at the CASPT2N/6-31G** level. It was found that the rate for the biradical was depressed by a factor of approximately 14 due to an increased activation energy relative to the reference radical. An extra energetic increment in E_a, corresponding to most of the singlet−triplet splitting in the biradical, served to slow radical-like reactions by the singlet ground-state biradical. Qualitatively, the energetic stabilization of the singlet biradical by through-bond coupling must be repaid as one "uncouples" (to use valence-bond language) the two nominally nonbonding electrons in *p*-benzyne to perform an abstraction reaction. The present results for the 9,10-dehydroanthracene biradical constitute the first clear experimental verification of both the qualitative and computational prediction that singlet biradicals are inherently poor hydrogen abstraction agents. This generalization has not been commonly considered in discussions of the action of the enediyne antitumor antibiotics. For example, with such a slow abstraction rate, competing reactions, like the retro-Bergman reaction in the current example, become important. More interesting is the notion that the biradical might live long enough to show selectivity in its chemistry, either by way of differential rates of reaction with different hydrogens or even possibly by way of equilibration between different binding sites or orientations for the *biradical*. It is important to realize that in *p*-benzyne itself, and the 9,10-dehydroanthracene biradical, the two radical sites are identical by symmetry, so that the only way in which the orbitals are split, and a singlet ground state induced, is by either through-space or through-bond coupling. In the natural products, the *p*-benzyne biradicals are asymmetrically substituted, which, by breaking the degeneracy of the orbitals, should give a larger singlet−triplet splitting. The larger singlet−triplet splitting would lead, in turn, to an even larger rate depression for abstraction reactions. Structural changes which affect the singlet−triplet splitting by increasing or decreasing through-bond and/or through-space coupling, e.g. inductive electron withdrawal on the σ-framework or steric compression of the radical-to-radical distance, should allow a rational modulation of hydrogen abstraction rates by remote substitution. The anthracene framework of **1** lends itself well to a systematic exploration of substituent effects on hydrogen abstraction rates. These studies are underway.

It remains only to comment upon some of the prior work that pertained to this biradical and related systems. Two prior reports, mentioned in the Introduction, claimed to have also found evidence for the 9,10-dehydroanthracene biradical as a reactive intermediate. Chapman *et al.*[8] photolyzed 9,10-anthraquinodiketene in low-temperature glasses and matrices, observed radical trapping products upon warming to room temperature, and most importantly, reported an UV/vis absorption spectrum that they assigned to the biradical. Both our group[38] and another group working independently[39] have been unable to produce a trappable biradical from either anthraquinodiketene or *p*-quinodiketene[40] as photochemical precursors to

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(29) Schmidt, H.; Schweig, A.; Krebs, A. *Tetrahedron Lett.* **1974**, 1471. Bieri, G.; Heilbronner, E.; Kloster-Jensen, E.; Schmelzer, A.; Wirz, J. *Helv. Chim. Acta* **1974**, *57*, 1265. Carlier, P.; DuBois, J. E.; Masclet, P.; Mouvier, G. *J. Electron Spectrosc.* **1975**, *7*, 55.

(30) Krebs, A.; Rüger, W.; Ng, L.; Jordan, K. D. *Bull. Soc. Chim. Belg.* **1982**, *91*, 363. Ng, L.; Jordan, K. D.; Krebs, A.; Rüger, W. *J. Am. Chem. Soc.* **1982**, *104*, 7414.

(31) Several computational studies are reviewed by: Krebs, A.; Wilke, J. *Top. Curr. Chem.* **1983**, *109*, 189.

(32) Bradshaw, J. D.; Solooki, D.; Tessier, C. A.; Youngs, W. J. *J. Am. Chem. Soc.* **1994**, *116*, 3177. Gleiter, R.; Ritter, J.; Irngartinger, H.; Lichtenthäler, J. *Tetrahedron Lett.* **1991**, *32*, 2883 and references therein.

(33) Toshima, K.; Ohta, K.; Ohtake, T.; Tatsuta, K. *Tetrahedron Lett.* **1991**, *32*, 391.

(34) Sugiyama, H.; Yamashita, K.; Fujiwara, T.; Saito, I. *Tetrahedron* **1994**, *50*, 1311.

(35) Myers, A. G.; Dragovich, P. S.; Kuo, E. Y. *J. Am. Chem. Soc.* **1992**, *114*, 9369.

(36) Concurrent biradical and ionic trapping products from α,3-dehydrotoluene, independently prepared by the photolysis of the (*m*-diazoniumphenyl)acetate inner salt support the observation of dual reactivity in ref 35. Logan, C. F. Ph.D. Thesis, Harvard University, 1996.

(37) The most complete and consistent set of absolute rate constants for phenyl radical come from: Scaiano, J. C.; Stewart, L. C. *J. Am. Chem. Soc.* **1983**, *105*, 3609. There are several other determinations as well which give similar numbers: Janzen, E. G.; Nutter, D. E., Jr.; Evans, C. A. *J. Phys. Chem.* **1975**, *79*, 1983. Kryger, R. G.; Lorand, J. P.; Stevens, N. R.; Herron, N. R. *J. Am. Chem. Soc.* **1977**, *99*, 7589.

(38) Kim, Y.-M. Diplomarbeit, ETH Zürich, 1995.

(39) Sander, W. Private communication.

the 1,4-biradicals. The absorption spectrum in the original report, assigned in that work to **1**, does not match the spectrum for the fast transient in the present report. It more closely resembles the spectrum of the slow transient, but the quality of the data really does not permit a definitive statement. The report by Darby *et al*.[9] of trapping products from **1** in the attempted preparation of **3** is, as discussed above, completely consistent with the present experimental study. It would be interesting to attempt to measure the rates coming from the direction **3** → **1** rather than **1** → **3** but that is beyond the scope of this investigation. One final piece of prior work deserves comment. Johnson and Bergman[41] prepared a propellane, going by a longer synthetic route involving the Ag^+-catalyzed rearrangement of bicyclopropenyls to Dewar benzenes, which would have given anthracene and *p*-benzyne. Upon thermolysis, though, their propellane underwent a complicated skeletal rearrangement to benzfluoranthene, which was attributed to an initial Cope rearrangement involving one of the isolated double bonds of the propellane. Upon photolysis, evidence was found for prismane formation by intramolecular $2\pi_s + 2\pi_s$ cycloaddition of the two isolated double bonds in the propellane. The difference between the propellane precursors **2** and the closely related compound in Johnson and Bergman's work occurs because, in the dibenzo compounds such as **2**, aromaticity in the fused benzenoid moieties would be sacrificed in going through either the Cope rearrangement or the intramolecular cycloaddition, thus disfavoring the unproductive reactions.

Conclusion

We report the first experimental determination of absolute rates of hydrogen abstraction by biradicals related to the *p*-benzyne-based DNA-cleaving agents. In comparison to the analogous rates by phenyl or 9-anthryl radical, the 9,10-dehydroanthracene biradical abstracts hydrogens more slowly by two orders of magnitude. The slow hydrogen abstraction reaction allows other chemical processes to compete, namely a kinetically significant reversibility of the Bergman reaction, for which qualitative evidence has recently appeared. Rationalization of the rate depression in biradicals in terms of through-bond coupling suggests structural changes which may allow the synthetic chemist to tune the reactivity of biradical-based DNA-cleavage agents.

Acknowledgment. The authors would like to thank Prof. Dr. W. H. Koppenol (ETH Zürich) for the use of the solution-phase flash photolysis spectrometer. Helpful suggestions from Prof. W. v. E. Doering (Harvard) are also acknowledged. This work was supported financially by the ETH Zürich and the Kontaktgruppe für Forschungsfragen (Basel).

JA960181Y

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(40) Marquardt, R.; Sander, W.; Laue, T.; Hopf, H. *Liebigs Ann*. **1995**, 1643.

(41) Johnson, G. C.; Bergman, R. G. *Tetrahedron Lett*. **1979**, 2093.