On the Mechanism of Quinone Formation from the Bergman Cyclization: Some Theoretical Insights

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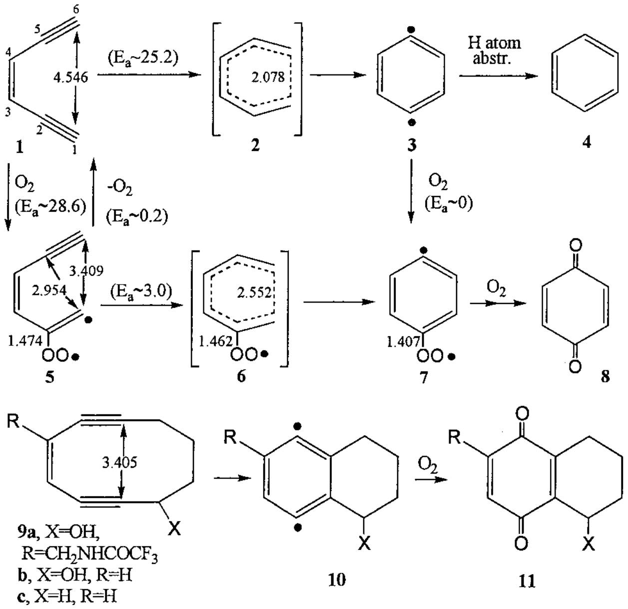
Introduction

The Bergman cyclization reaction[1] continues to be of tremendous interest to organic and biological chemists alike. Such interest stems from the potency of natural enediyne antitumor antibiotics such as calicheamicin g_1, dynemycin A, and esperamicin A_1[2] and has prompted numerous efforts to theoretically understand[3] and synthetically manipulate[4] the substrates for this reaction. The prototypical Bergman cyclization involves the conversion of an enediyne (**1**) to a *p*-benzyne (**3**), followed by H atom abstraction (normally from an efficient H donor such as 1,4-cyclohexadiene) to produce, ultimately, an arene (**4**). Another potential pathway, previously effected only with chemical oxidants,[4c] is interception by O_2 to form a peroxyl diradical (**7**) and, ultimately, a quinone (**8**).



A recent and significant paper reported the antibody-catalyzed conversion of cyclic enediyne **9a** to quinone **11a**.[5] It is noteworthy that the quinone product showed greater cytotoxicity than the precursor enediyne. Of additional importance is the fact that, in buffered water alone (no antibody), instead of the expected reduced benzene, quinone **11a** was again the product. Intriguingly, the authors found that the rate of quinone formation was *proportional to the dissolved O_2 concentration*, with no formation of **11a** under degassed conditions. This led them to suggest that O_2 was reacting with *p*-benzyne **10a** to give **11a**. However, the origin of the O_2 rate dependence remains unknown. Two obvious possibilities are that (a) reaction of O_2 and **10a** is rate determining and (b) O_2 reacts directly with enediyne **9a**, followed by cyclization, thereby circumventing the *p*-benzyne intermediate.[6] Given these ambiguities, we have conducted density functional theory (DFT) studies on the oxygen-mediated reaction and conclude that neither of these possibilities appears to be likely.

Computational Methods

All calculations reported herein were effected using the Gaussian 98[7] suite of programs at the UBLYP/6-31G* level[8] of DFT for triplets and singlet biradicals and at the BLYP/6-31G* level for closed shell singlets, unless specified otherwise. We chose to use the BLYP functional not only so that comparisons with previous work[3a,9] could be made but also because we have found that the recommendation that UB3LYP is preferable to UBLYP, which was based on results for the parent system,[10] is not generally true. As we[3a] and others[9] reported, the relative energies of *p*-benzynes are more overestimated by UBLYP/6-311+G** than by UBLYP/6-31G*. The former basis set is preferred, however, because it does a better job (very close to experiment) on the cyclization activation energies. For example, the calculated BLYP/6-31G* (BLYP/6-311+G**) values for **9c** are $\Delta H^* = 20.2$ (23.7) kcal/mol and $\Delta G^* = 21.8$ (25.3) kcal/mol, while the published experimental activation energy is 23.8[11]

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(24.0[12]) kcal/mol. Relative barriers, which are the focus of this paper, are modeled well using even the 6-31G* basis set, which we have used primarily in this work.

It must be realized that calculations of O_2 energies are quite difficult, and accurate results require multireference CI calculations.[13] As an indication of this, DFT finds the lowest singlet state of O_2 to be 9.1 kcal/mol (UBLYP/6-31G*) and 10.4 kcal/mol (UB3LYP/6-31G*) above the triplet ground state, as compared to the experimental value of about 23 kcal/mol. However, the $\langle S^2 \rangle$ values for the singlet are 1.0 in both cases, which indicates that the state found is half singlet and half triplet. Correction for this places the singlet state 18.2 kcal/mol (UBLYP) and 20.8 kcal/mol (UB3LYP) above the triplet, which is respectable. While these values do not improve with larger basis sets, CCSD(T) does no better (corrected singlet−triplet gap of 19.6 kcal/mol). On the other hand, the bond distance is fairly well calculated (BLYP, 1.240 Å; B3LYP, 1.215 Å; expt, 1.208 Å). Interestingly, the CCSD(T) calculations give slightly lower energies for the BLYP-optimized bond distance than for the B3LYP-optimized distance. It appears as if the absolute energy of O_2 should be somewhat lower than that given by our calculations, as is also true for the *p*-benzynes. The main point, however, is that these errors should be carried throughout the diradical calculations, which suggests that the derived relative energies should be accurate; validation of this has appeared recently.[14]

The polarized-continuum model (PCM) was used to calculate the effect of bulk water solvent in some instances.[15] Singlet oxygenated biradical energies were always at least somewhat higher than the calculated triplet energies, including those for **7**. Supporting Information contains complete geometry and energy information for all species studied.

Results and Discussion

To be kinetically second order, the barrier for reaction of **10a** with O_2 must be at least about equal to the cycloreversion barrier to **9a**. Otherwise, a first-order rate dependence for the disappearance of **9a** (appearance of **11a**) should be observed, irrespective of whether O_2 is present to trap **10a** or the relative trapping efficiency of O_2. The calculated (BLYP/6-311+G**) reversion barrier for **10c** was reported to be 9.6 kcal/mol;[3a] recalculation of this value at UBLYP/6-311+G** for **10c** now gives 10.8 kcal/mol, and correction for the overestimation of the energy of **10c** (on the basis of the similar overestimation of **3**) gives a realistic reversion barrier of ca. 18 kcal/mol. This is ca. 2 kcal/mol less than the calculated (13.1 kcal/mol) and experimental[16] (20.2 kcal/mol) reversion barrier for **3**. The barrier for reaction of **3** with O_2 was explored on the triplet surface on a point-by-point basis by fixing the C−O distance while optimizing all other geometric parameters. The results are shown graphically in Figure 1. Not surprisingly, there is no calculated enthalpic barrier. At $r_{CO} = 4.0$ Å, the geometry is fully that of the separated O_2 and **3** components. The energy starts dropping around $r_{CO} = 3.0$ Å, leading to the diradical **7**, which is about 45.5 kcal/mol lower in energy (43.0 kcal/mol lower in enthalpy) and 32.2 kcal/mol lower in free energy at 298 K (due to the large negative entropy component). Of course, there is an actual barrier due to the entropy component. As has been discussed in detail for other entropy-controlled reactions (such as carbene additions), the actual variational transition state will occur at an apparently negative enthalpy because of the steep enthalpy drop once the reaction starts.[17] Thus, one can expect a real barrier of about 10 kcal/mol at 298 K. Since there is no expectation that the situation is any different for **10** + O_2, *this level of theory does not support the idea that* **10** *could react with* O_2 *in a kinetically meaningful step*.

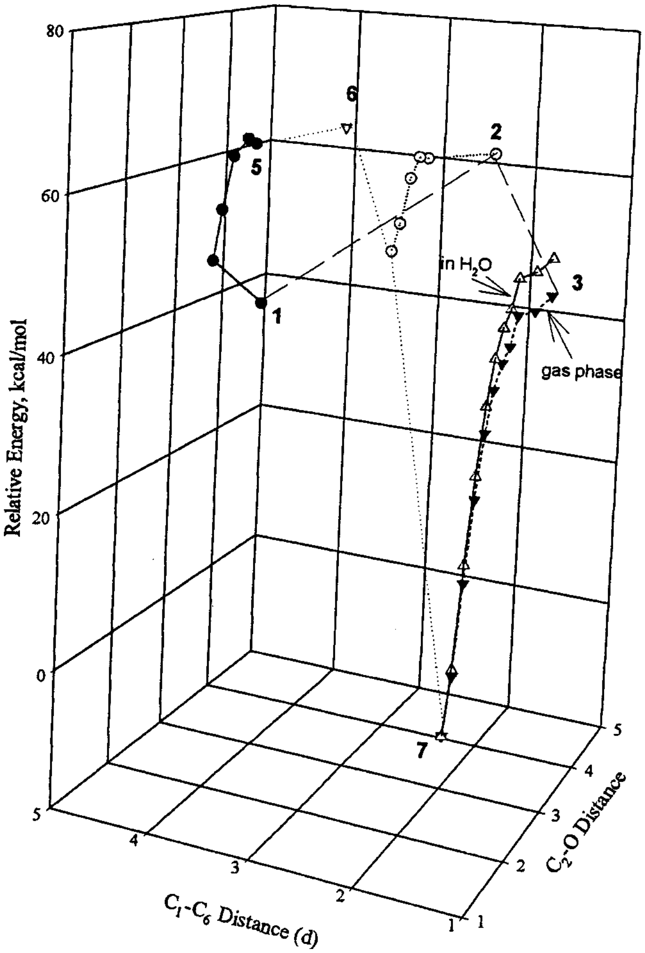

Figure 1. Electronic energies of species involved in the cyclization of **1** with and without O_2. Note that all energies include the energy of O_2 and are directly comparable as a result.

Also, it does not appear possible that a rate-determining step involving O_2 could occur after the formation of adduct **13**. Since **13** is a phenyl radical (possibly in resonance with a carbene-carbonyl ylide structure, which should be at least as reactive), it also would be expected to react with O_2 with only an entropic barrier (note that triplet **13** can react with $^3O_2$ to give a singlet product; no intersystem crossing is required). This is similar to the fact that, in the conversion of *p*-benzyne to benzene, the second H atom abstraction goes faster than the first.[18] The double adduct of O_2 to **10**, which is a bis-carbonyl ylide, should lie far below the cyclization transition state for the formation of **10**. As a model, the energy (BLYP/

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6-31G*) of the double-O_2 adduct to the parent system (**3**) lies about 111 kcal/mol below the energy of **2** + $2O_2$. Thus, any subsequent rate-determining step would have to be activated by over 100 kcal/mol, which is grossly incompatible with the experimental conditions. We are not in a position to specify the steps by which the bis-carbonyl ylide is converted into the final quinone product. If it is not a catalyzed process, it may involve reaction with additional molecules of O_2. Another alternative would be a bimolecular-type process in which two bis-carbonyl ylides come together to generate a linear structure with four contiguous oxygen atoms, followed by loss of O_2 (presumably singlet) and consequent generation of two carbonyl groups. As an analogy for this, we found that a cyclopropanone ylide (formed from the reaction of an α-bromocyclopropyllithium with O_2) gave cyclopropanone, in the *absence* of O_2, via a process that could be accelerated by the presence of a reducing agent.[19] In this case, the carbonyl ylide-to-ketone reaction occurred around −78 °C, which strongly suggests that such a process would be fast (i.e., not rate determining) in the conversion of **9** to **11**.

However, the possibility that the aqueous solvent alters the picture so far presented has to be considered. This was done in two ways. First, the energies of each of the gas-phase geometry points for the approach of $^3O_2$ to *p*-benzyne **3** was evaluated in H_2O solvent using the PCM. The resulting energies are included in Figure 1. Because the nonpolar $^3O_2$ is destabilized by solvation and the polar adduct, **7**, is stabilized, the overall energy change in H_2O is about 5 kcal/mol greater than that in the gas phase. However, there is still no activation barrier to reaction. The second approach was to search for a specific $^3O_2$−water hydrogen-bonded complex. If such a complex exists, it might require an activation barrier to break the hydrogen bond(s) prior to or during its reaction with **3**. Water oligomers have been observed experimentally[20] and calculated theoretically,[21] including via DFT. With BLYP/6-31G*, we found a water dimer that is 8.3 kcal/mol below the sum of two separate water molecules. This value represents the sum of a hydrogen bond plus a ca. 1 kcal/mol basis set superposition error, which we did not eliminate. A “complex” of $^3O_2$ and $(H_2O)_2$ was similarly found at 8.3 kcal/mol below the sum of its parts; the distance between the molecular oxygen and any part of the water was over 2 Å. A more stringent test was provided by an attempt to find a complex starting from a cyclic array of four water molecules and $^3O_2$. As shown in Figure 2, when this “supermolecule” was optimized, the $^3O_2$ was squeezed out of the array to generate one of the water tetramer isomers, with the $^3O_2$ over 2.6 Å away; the energy of the supermolecule was consistent with having four hydrogen bonds. Thus, $^3O_2$ does not form specific hydrogen bonds that would hinder its reaction with **3**, a result which is consistent with the PCM calculations.

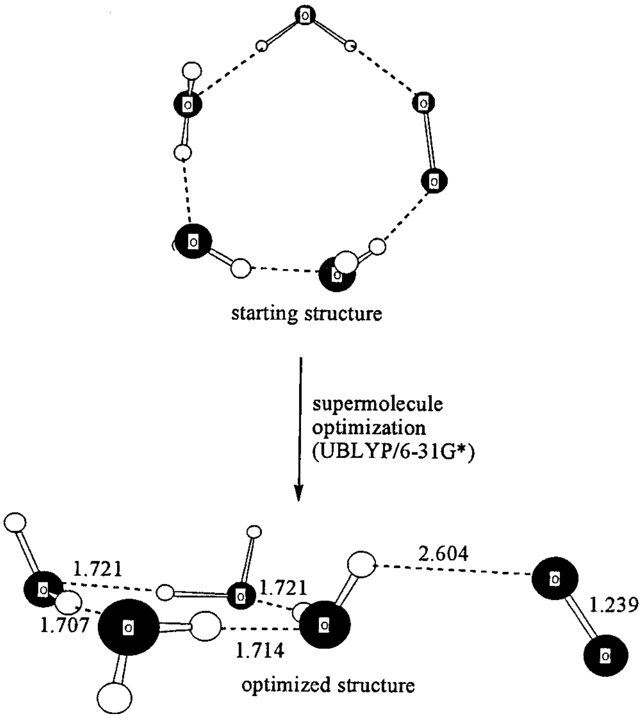

Figure 2. Result of $^3O_2$ inclusion in $(H_2O)_4$ supermolecule calculation. Note that the UBLYP/6-31G*-calculated oxygen−oxygen distance in $^3O_2$ is 1.2395 Å.

We next investigated the possibility of a direct reaction of $^3O_2$ with an enediyne to generate the *p*-benzyne−O_2 adduct. In principle, it is possible that $^3O_2$ would react with the enediyne, which would then cyclize, or that $^3O_2$ might intercept a partially cyclized enediyne before it reaches the (unaided) transition state. While the former possibility would be favored by the lower energy of the enediyne, the slight development of diradical character as the Bergman cyclization transition state is approached might favor the latter pathway (note that such diradical character must be quite minimal, as the transition state is extremely well modeled by a restricted wave function). This might be more important for the strained cyclic enediyne structure of **9**. In addition, the possibility of hydrogen-bonding assistance by the hydroxyl group of **9a** (**9b**) had to be considered. We first examined the reaction of $^3O_2$ with **1** and with **2**; the results are shown graphically in Figure 1, and the key data are included with the structural drawings. Close approach of $^3O_2$ at all points prior to the Bergman cyclization transition state (**2**) requires more energy (not even counting the entropy) than formation of **2** itself. Addition of $^3O_2$ to **1** can occur but requires about 3.5 kcal/mol more electronic energy than cyclization of **1**. Moreover, the $^3O_2$ adduct, **5**, is bound by only ca. 0.2 kcal/mol; inclusion of entropy would lead to no binding for **5**. Once “formed”, **5** can cyclize via transition state **6** with very little further activation, although this entire process is moot for the parent system due to entropy (not to mention the fact that closely related radicals cyclize in an exo-5-dig fashion[3c] via attack at the closer acetylenic carbon (see structural drawings for distances)).

The situation is a bit different for the cyclodecenediyne case.[22] We found two $^3O_2$ approach orientations to **9c**:

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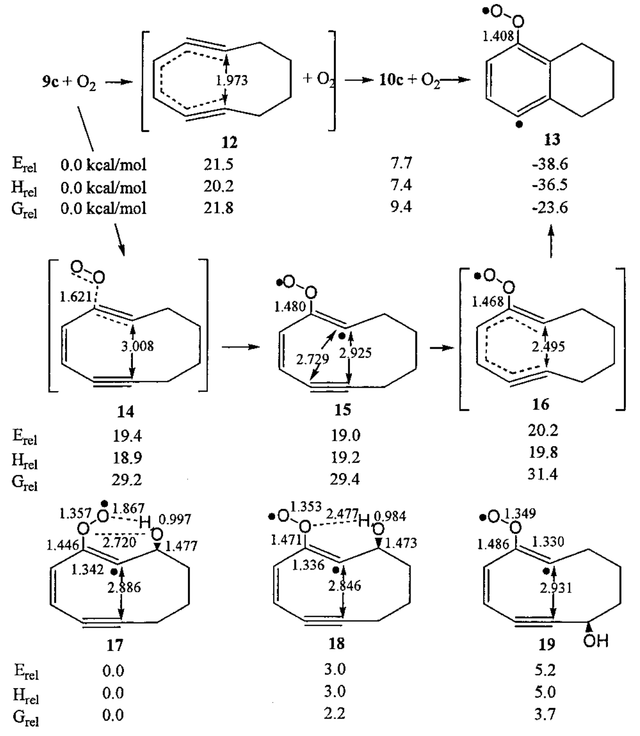
[22] The deoxygenated structures (“**c** series”) were used in place of the hydroxy compounds (“**b** series”) for calculational speed, except when there may have been some direct effect of the hydroxyl group expected (e.g., hydrogen bonding).



coplanar, s-cis to the developing vinylic radical (not shown), and coplanar, s-trans to the same (**14**). The latter is on the order of 1 kcal/mol lower in energy. We also located the cyclization transition state (**16**) from the s-trans diradical (**15**) to the corresponding oxygen−*p*-benzyne adduct (**13**, which is ca. 3 kcal/mol more stable than its 180° rotamer). As shown on the structural diagrams, **15** is barely or not bound but lies about 1 kcal/mol below the unaided Bergman cyclization transition state (**12** + $^3O_2$). Also, **16** lies barely below **12** + $^3O_2$ enthalpically (H_{rel}). However, when entropy (at 298 K) is taken into account (G_{rel}), it is seen that the oxygenated cyclization pathway requires about 10 kcal/mol more energy than the $^3O_2$-independent cyclization pathway. This appeared to preclude $^3O_2$ involvement in the reaction in a kinetically meaningful step. However, what about a strong hydrogen-bonding effect due to the propargylic hydroxyl in **9a**?

After preliminary calculations of hydrogen bonding in a propargyl alcohol (the $^3O_2$ adduct showed that an effect could be seen[23] and that an additional H_2O molecule formed only a hydrogen bond to the hydroxyl group rather than, for example, a bridged structure that would additionally stabilize only a propargylic adduct), we studied the $^3O_2$ adducts of **9b**. The three structures that were found, **17**−**19**, are shown with relevant bond distances and relative energies. It is interesting that **18** shows hydrogen-bonding effects not only energetically but also in the diminished H···O distance of 2.477 Å vs the 2.720 Å distance seen in **17**. In any event, the maximum effect in G_{rel} (**17** vs **19**) is only 3.7 kcal/mol. This would still leave the $^3O_2$ adduct cyclization pathway at least 6 kcal/mol above the $^3O_2$-independent pathway. Since this value is more than the likely relative errors, *we conclude that preliminary oxygenation of enedynol **9a**, followed by cyclization, is highly unlikely and an explanation for the kinetic observations reported likely lies elsewhere.*

Alternate pathways may be suggested for reaction of benzyne **10a** in an oxygenated aqueous environment, but it is not obvious how such pathways could render the reaction of **10a** rate determining. A plausible process would be one that catalyzes the reaction of enediyne **9a**. For example, adventitious metal ions in the medium could play a role in the O_2-dependent production of HO radicals, which then react in a rate-determining step with **9a**. Given the significance of a direct enediyne-quinone pathway, coupled with the spectacular antitumoral activity of quinone metabolites,[5] additional studies, including labeling experiments, are in order to clarify the origin of the oxygen atoms in **11a**.

Supporting Information Available: Cartesian coordinates and energies for all stationary points and intermediate points studied. This material is available free of charge via the Internet at http://pubs.acs.org.

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[23] We are unaware of calculations of hydrogen bonding to a peroxyl radical.