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Ab Initio Calculation of Hydrogen Abstraction Reactions of Phenyl Radical and *p*-Benzyne

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We report a comparison, based on *ab initio* computational methods, of the reactivity of the *p*-benzyne biradical **1** versus the phenyl radical **2** as a model for the hydrogen abstraction ability of the putative intermediates in the enediyne family of antitumor antibiotics.[1] In the original members of the enediyne family of agents, Bergman cyclization[2] had always been much slower than any of the subsequent reactions of the biradicals, making those latter steps kinetically unobservable. The common assumption had been that the rate of hydrogen abstraction by the arene biradicals would be comparable to that for **2**. Recently, a model compound representing the C-1027 chromophore, a kedarcidin analog, has been shown[3] to exhibit kinetics consistent with roughly comparable rates of Bergman cyclization and subsequent hydrogen abstraction. In that work, the rate of hydrogen abstraction by **2**, with an arbitrarily chosen correction for steric interactions, was used explicitly as an estimate for the rate of abstraction by the biradical. Given the dearth of kinetic data on biradicals, the assumption is unsurprising, but simple theoretical considerations (see below) do suggest that **1** should be less reactive than **2** on electronic grounds, perhaps by a factor of 10 or more. The present computational work confirms this expectation and suggests ways in which the reactivity of *p*-benzyne-like biradicals may be tuned rationally to optimize reactivity and/or selectivity.

All calculations were performed using the Gaussian 92 and MOLCAS-3 programs[4] on an IBM RS/6000-590 workstation. As a model for hydrogen abstraction by **1** or **2** from deoxyribose at the 4′ or 5′ positions, the activation energy for hydrogen abstraction from methanol was computed at the CASPT2N/6-31G**//CAS/3-21G level of theory. Inclusion of dynamic electron correlation by way of the MBPT2 correction to a multireference CASSCF wave function has been demonstrated to be crucial to the accurate modeling of bond-making and bond-breaking processes.[5] The general methodology involved constrained optimization of the geometry at series of points at the CAS(4×4) level for abstraction by **1** and CAS(3×3) for abstraction by **2** with a small basis set, followed by single-point energy calculations at those geometries at the CASPT2N level with the same active space and a much bigger basis set. The active space comprised of the one or two nonbonding orbitals on the arene fragment and the C−H σ and σ^* orbitals on the methanol. In this approach, necessitated by the absence of analytic gradients in the CASPT2N method, the transition state was found manually on a two-dimensional potential surface in which the two respective C−H bond lengths in the supermolecule, i.e., benzyne (or phenyl)-to-H and hydroxymethyl-to-H, entered parametrically at each point and the other geometric parameters were allowed to relax. Some geometric constraints had to be placed on the system to facilitate identification of the orbitals in the active space and to speed computation: (i) the aromatic ring was constrained to *local* C_{2v} symmetry, (ii) the C···H···C axis was held to linearity, and (iii) the hydroxymethyl fragment was constrained to local C_s symmetry with the C−O−H plane bisecting and perpendicular to the arene ring. The latter geometric constraint was lifted at the last stage of calculation to allow for stabilization of the incipient hydroxymethyl radical center by interaction with an oxygen lone pair. Each surface was characterized by approximately 150 single-point calculations (at relaxed geometries) at 0.1 Å steps in each of the C−H bond lengths, with the step size tightening to 0.025 Å in the region near each transition state. The geometries of **1** and **2** in the supermolecule at the asymptotic limit in the reactant channel (10 Å out) were essentially the same as independently produced geometries for **1** and **2** at higher levels of theory.[6−9] The singlet−triplet splitting for **1**, 4.1 kcal/mol at the CASPT2N/6-31G** level, is somewhat higher than that calculated by Nicolaides and Borden[7] (1.8 kcal/mol) and Wierschke, Nash, and Squires[8] (2.2 kcal/mol), but that is understandable in that the latter two groups used correlation-consistent methods that would minimize overestimation of the triplet energy. The computed exothermicity for the homodesmotic region involving singlet **1**, $2C_6H_5 \rightarrow C_6H_6 + C_6H_4$, is $\Delta H = -2.8$ kcal/mol at our level of calculation, which lies within the error bounds of the value using experimentally-determined heats of formation ($\Delta H = 5.3 \pm 3.4$ by Wenthold and Squires[10]).

The qualitative picture justifying an expectation of lowered reactivity in singlet biradicals with regard to hydrogen abstraction derives from either valence bond promotion energy[11,12] or valence bond curve-crossing[13] models. In short, the hypothetical "noninteracting" biradical is identified (approximately) with the triplet biradical, below which the singlet lies due to some interaction between the radical sites. In the present case, the close correspondence between the 2.8 kcal/mol exothermicity in the homodesmotic reaction above, and the computed singlet−triplet gap of ∼2 kcal/mol, support this interpretation. One would expect the "noninteracting" *p*-benzyne (≈triplet **1**), *by definition*, to show essentially the same abstraction rates as does the phenyl radical. Accordingly, the actual singlet biradical **1**, for which the stabilization energy must be repayed at least in part at the transition state, should abstract hydrogens more slowly. An upper bound on the elevation of the activation energy would be the entire singlet−triplet gap, which in **1** is a

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(10) Wenthold, P. G.; Squires, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 6401 reports $\Delta H_{f,300}[\mathbf{1}] = 137.3 \pm 3.3$ kcal/mol. For the homodesmotic reaction, we used $\Delta H_{f,300}[\mathbf{2}] = 81.2 \pm 0.6$, from: Davico, G. E.; Bierbaum, V. M.; DePuy, C. H.; Ellison, G. B.; Squires, R. R. *J. Am. Chem. Soc.* **1995**, *117*, 2590.

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(12) A good discussion, with some historical notes, of the valence state and valence promotion energy arguments can be found in the following: Murrell, J. N.; Kettle, S. F. A.; Tedder, J. M. *The Chemical Bond*, 2nd ed.; John Wiley & Sons: New York, 1985; pp 247−249. More recently, the concept has been resurrected, most notably by Goddard and co-workers. For an example concerning carbenes, see: Carter, E. A.; Goddard, W. A. *J. Phys. Chem.* **1986**, *90*, 998. See also: Simons, J. P. *Nature* **1965**, *205*, 1308.

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modest 2 kcal/mol. Such a difference in E_a corresponds nevertheless to a rate depression at room temperature by a factor of 30.

We find moderately early transition states for both abstractions, with the arene C−H and methanol C−H bond distances at 1.375 and 1.275 Å for both [**1** + methanol] and [**2** + methanol]. The local geometries at both the arene and methanol moieties remain almost unchanged from unperturbed molecules. The optimum dihedral angle between C···H···C axis and the methanolic O−H bond was found to be ∼60° in both reactions, indicative of antiperiplanar overlap of an oxygen lone pair with the σ^* orbital of the breaking bond. The transition state was found to lie 9.53 (for **1**) and 7.95 (for **2**) kcal/mol above the separated reactants, indicating that approximately two-thirds of the singlet stabilization energy appears as an extra increment to the activation energy in reactions of **1**. The computational results suggest that the room temperature rate of hydrogen abstraction by **1** should be ∼14 times slower than that for **2**. Parenthetically, the computed activation energy for hydrogen abstraction from methanol by the phenyl radical is consistent with experimental determinations of phenyl radical abstraction rates[14] from THF, if one accounts for the slightly stronger C−H bond in methanol. Moreover, the crux of the argument derives from the *comparison* of phenyl to *p*-benzyne rates, and, given the similar geometries and frequencies for the reactants and transition states in the two series, one would expect that the difference in activation energies ought to persist going to higher levels of theory.

Further computation and experimental studies are underway to confirm this picture. In particular, because the modest singlet−triplet gap in **1** is due to through-space and through-bond effects working in opposite directions, one can imagine minor perturbations such as a small compression or stretching of the benzyne ring having an effect on the rate or abstraction. Preliminary computational results indicate that, as expected, a C1−C4 compressed benzyne has a smaller singlet−triplet gap and a lowered activation energy abstraction, while a stretched benzyne shows just the opposite behavior. We would also predict that a larger perturbation, such as introduction of a heteroatom to make 2,5-dehydropyridine, for example, would increase the singlet−triplet gap and lead to a less reactive, and perhaps more selective, biradical. Studies in this direction will be the subject of future reports.

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Supporting Information Available: Geometries and absolute energies at the reactant asymptote and the transition states for hydrogen abstraction by **1** and **2** (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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