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Quantum Chemical Characterization of the Cyclization of the Neocarzinostatin Chromophore to the 1,5-Didehydroindene Biradical

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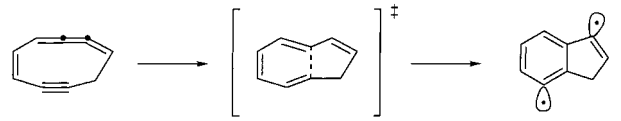
ABSTRACT



Quantum mechanical calculations have been carried out for the cyclization of the neocarzinostatin chromophore cyclonona-1,2,3,7-tetraen-5-yne to 1,5-didehydroindene. The 298 K reaction activation enthalpy, exothermicity, and singlet–triplet splitting (H_0) of the product biradical are predicted to be 17.8, 1.2, and −6.4 kcal/mol, respectively, at levels of theory showing near-quantitative agreement with experiment for the analogous cyclizations of hex-3-ene-1,5-diyne and hepta-1,2,4-trien-6-yne. Factors controlling differences in the Myers–Saito cyclization compared to the Bergman cyclization are analyzed.

Members of the enediyne class of antitumor/antibiotics undergo Bergman cyclization[1] to generate highly reactive *p*-benzyne biradicals that effect double-stranded cleavage of DNA.[2] Another antitumor/antibiotic, neocarzinostatin,[3,4] acts by an analogous mechanism, but in this case the biradical is generated from the Myers−Saito cyclization[5,6] of a cyclononatetraenyne to yield a 1,5-didehydroindene (DDI). Using levels of theory benchmarked against the experimentally characterized[7,8] Bergman cyclization of hex-3-en-1,5-diyne (HED) to *p*-benzyne (reaction **a**, Scheme 1), we report here the first accurate calculation of the cyclization thermochemistry of cyclonona-1,2,3,7-tetraen-5-yne (CNT) to 1,5-DDI (reaction **b**, Scheme 1); in addition, we compute the singlet−triplet (S−T) splitting for 1,5-DDI, benchmarking the theory against the experimentally characterized[9] S−T splitting for *p*-benzyne. Comparisons are also made to the analogous cyclization of acyclic hepta-1,2,4-trien-6-yne (HTY; reaction **c**, Scheme 1) for which experimental data[5,10,11] and results from prior computational studies[10−15] are available.

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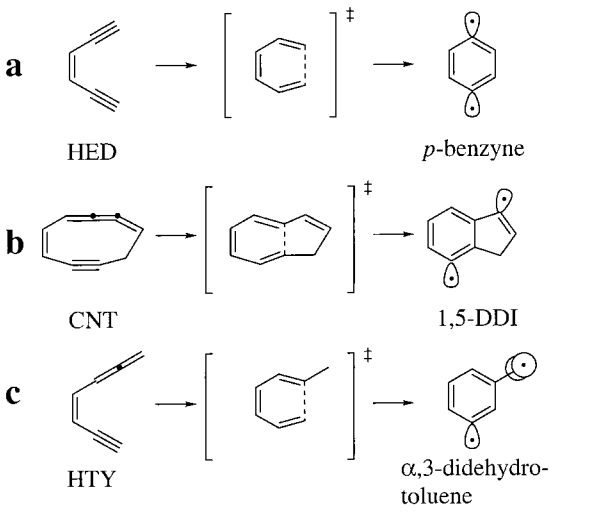
Table 1. Biradical S−T Splittings (H_0) and Relative Enthalpies (H_{298}) of Stationary Points for Reactions **a**, **b**, and **c**[a]

reacn	source of energies	uncyclized educt	cyclization TS structure	singlet biradical[b]	S−T splitting
a	BD(T)[c]	0.0	25.6	4.8	−4.5
	SAC-BD(T)	0.0	27.1	8.5	
	exptl	0.0	28.2 ± 1.1[d]	8.5 ± 1.0[d,e]	−3.8 ± 0.4[f]
b	BD(T)	0.0	15.6	−4.4	−7.1
	SAC-BD(T)	0.0	16.7	−1.2	
	best estimate[g]	0.0	17.8	−1.2	−6.4
c	BD(T)	0.0	19.5		
	SAC-BD(T)	0.0	20.6		
	exptl	0.0	21.8 ± 0.5[h]	−15.0 ± 4.0[i]	

[a] All units kcal/mol. BPW91/cc-pVDZ geometries. [b] Absolute energies for computed rows in this column (hartrees) are as follows. H_0: −230.151 53; −230.098 98; −345.303 52; −345.227 45; −269.334 59; −269.279 03; (H_{298} − H_0) for *p*-benzyne is 0.005 48, for 1,5-DDI is 0.007 56, and for α,3-didehydrotoluene is 0.008 72. [c] Reference 21. [d] Reference 7. [e] Reference 8. [f] Reference 9. [g] See text; error bars of ±2 kcal/mol would be reasonable. [h] Reference 5. [i] References 10 and 11.

All calculations employed the cc-pVDZ basis set.[16] Electronic energies were computed from coupled-cluster calculations employing Brueckner orbitals that included double excitations and a perturbative estimate for triple excitations (BD(T)).[17] Brueckner orbitals eliminate contributions from single excitations in the coupled cluster ansatz, and this alleviates instabilities[18] associated with very large singles amplitudes in the more common CCSD(T) method[19,20] that have been observed in aromatic biradicals having low degrees of symmetry.[21]

Scheme 1



Geometries were optimized at the density functional level of theory, using the gradient-corrected functionals of Becke[22] and Perdew et al.[23] (BPW91). Thermal enthalpy contributions were computed from harmonic vibrational frequencies at this level. For the singlet biradicals, the geometry was optimized, allowing the DFT "wave function" to break spin symmetry; this has been shown to give more accurate geometries for a number of relevant aromatic singlet biradicals,[21,24,25] and test calculations on 1,5-DDI found the unrestricted geometry to be 2.8 kcal/mol lower in energy than the restricted geometry at the BD(T) level. DFT geometries and frequencies in several related biradical systems have been shown to be of very high quality (and in particular better than multiconfiguration self-consistent field (MCSCF) geometries).[9,21,24−28] Although concerns about the ability of DFT to accurately predict the energetics of cumulenic systems have been expressed,[29] this does not appear to adversely affect the predicted geometry of cumulenic CNT. Multireference second-order perturbation theory (CASPT2) shows the DFT structure for CNT to be 1.3 kcal/mol lower in energy than the corresponding MCSCF structure.[30]

Results from all levels of theory are provided in Table 1, as are available experimental values. BD(T) results for reaction **a** are in fair agreement with experiment, but some discrepancies remain for the cyclization thermochemistry. Previous work on the Bergman cyclization and benzyne thermochemistry in general has shown that correcting for basis set incompleteness improves the accuracy of various theoretical predictions.[21,26,27] However, the size of the CNT/1,5-DDI system renders highly correlated calculations with a triple-ζ basis set impractical.[31] To correct the BD(T)/

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(31) Corrections computed as (MP2/cc-pVTZ − MP2/cc-pVDZ) were surveyed, but this level of theory was found to be very untrustworthy for the relative energies of the various stationary points, and the effects associated with basis set size were similarly unstable.

cc-pVDZ energies for remaining basis set *and* electron correlation effects, we make use of the scaling-all-correlation (SAC) method of Gordon and Truhlar.[32] The SAC−BD(T) energy is here defined as

$$E[\text{SAC-BD(T)}] = E[\text{HF/cc-pVDZ}] + \{E[\text{BD(T)/cc-pVDZ}] - E[\text{HF/cc-pVDZ}]\}/A \quad (1)$$

where A is a scale factor to be optimized. In the case of reaction **a**, we find the optimal scale factor (which minimizes the mean unsigned error for the forward activation enthalpy and endothermicity) to be 1.059, and that value is used here for reactions **b** and **c** as well.

An important feature of the SAC procedure in the present case is that the differential BD(T) correlation energies (and hence the effect of scaling) are very similar for the analogous stationary points in the different cyclizations. Thus, the corrections to the activation enthalpies and the overall thermicities brought about by scaling in the three systems differ one from another by no more than 0.5 kcal/mol. This suggests that the use of the same scale factor for all three reactions is well justified and, moreover, confirms that the natures of the bonding changes taking place in the three cyclizations are substantially similar.

Given these various similarities, we derive best estimates for the relative energies of the CNT cyclization stationary points and the S−T splitting of 1,5-DDI by correcting the SAC-BD(T) and BD(T) predictions, respectively, by the amount needed to bring those same levels of theory into quantitative agreement with the various experimental values listed in Table 1. Thus, the 298 K forward cyclization of CNT to 1,5-DDN is predicted to be exothermic by 1.2 kcal/mol with an activation enthalpy of 17.8 kcal/mol. Singlet 1,5-DDI is predicted to lie 6.4 kcal/mol below the corresponding triplet, suggesting that 1,5-DDI may be slightly less reactive as a hydrogen-atom-abstracting agent than *p*-benzyne, which has a S−T splitting of 3.8 kcal/mol. This latter observation is interesting, since in the didehydronaphthalene series an analogous ordering is observed for a transoid vs a cisoid biradical: the 1,5-splitting is somewhat larger than the 1,4.[33,34]

Other key similarities are also evident between reactions **a** and **b**. The predicted barriers to *retro*cyclization from the aromatic biradicals are within 0.7 kcal/mol of one another. Also, in both TS structures, the degree of biradical character is very low: the ratios of the two dominant configurations in CAS/cc-pVDZ wave functions are computed to be 95:5 and 93:7 for reactions **a** and **b**, respectively.[30]

Turning now to a comparison of reactions **a**−**c**, we first consider the activation enthalpies for **b** and its acyclic analogue **c**. Myers et al.[5] have measured the activation enthalpy for reaction **c** as 21.8 ± 0.5 kcal/mol in 1,4-cyclohexadiene as solvent (the good agreement between SAC-BD(T) and experiment suggests that solvation effects are minimal, as might be expected in so nonpolar a solvent). We ascribe the 4 kcal/mol reduction in activation enthalpy for reaction **b** primarily to ring strain present in CNT. This strain can be inferred from the optimized geometry of CNT, which includes a CCC bond angle of 155.2° at one alkyne carbon and another of 153.6° at an internal carbon of the cumulenic fragment; both angles would optimally be 180°.

Although it has a lower barrier, reaction **b** is less exothermic than **c** by about 14 kcal/mol. This difference is associated primarily with the π conjugation energy that is present in the α,3-didehydrotoluene σ,π-biradical but not the 1,5-DDI σ,σ-biradical. Koga and Morokuma[12] have estimated the conjugation energy of the former biradical to be 12.1 kcal/mol at the MCSCF level, which is a magnitude consistent with the present predictions (note that BD(T) calculations cannot be performed for the α,3-didehydrotoluene σ,π-biradical because it cannot be described by a single determinantal wave function).

Intrinsic differences between Bergman cyclizations and Myers−Saito cyclizations have been previously discussed within the context of reactions **a** and **c**. Hrovat et al.[35] have noted that the former reaction sacrifices two acetylene π bonds to create a new aromatic C−C bond while the latter sacrifices one acetylene and one allene π bond for the same C−C bond formation. The latter situation also holds for reaction **b** and, in the limit of complete π bond destruction, and in the limit of viewing a cumulene π bond as being equivalent in strength to ethylene, Hrovat et al.[35] suggest that this could account for up to 12 kcal/mol of additional exothermicity in Myers−Saito cyclizations compared to Bergman cyclizations. A cumulene π bond is actually stronger than an ethylene π bond (owing to the shorter C−C bond length resulting from the sp-hybridized carbon atom(s)), but this bond energy analysis clearly makes a significant contribution to the 9.7 kcal/mol greater exothermicity of reaction **b** compared to **a**. On the basis of smaller model systems, Koga and Morokuma[12] and Hrovat et al.[35] have also suggested that the greater stability associated with incipient formation of a transoid biradical, as in 1,5-DDI, compared to a cisoid one, as in *p*-benzyne, is an important factor influencing the cyclization energetics. The two groups propose a range of 3.8−12 kcal/mol for this effect. Our own computations of the S−T splittings in the two biradicals suggest that this difference is only 2.6 kcal/mol (this assumes the triplets in each case to have negligible biradical stabilization energies, an assumption borne out by experiment and computation on other aryne systems[9,26,33,34]). The sum of these two effects together with some ring-strain relief in the cyclization of CNT is clearly sufficient to explain all of the difference in reaction exothermicity for **b** compared to **a**. While the low degree of biradical character in the transition states might be interpreted to suggest that only a small fraction of this energy difference should be apparent in the activation enthalpies, nevertheless this difference in **a** compared to **c** is still 6.4 ± 1.3 kcal/mol (this comparison removes any influence from ring strain; note that in the

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transition state structure for reaction **c** there is negligible benzylic conjugation).

In summary, calculations at a level of theory calibrated to give near-quantitative agreement with experiment for the Bergman cyclization of hex-3-ene-1,5-diyne to *p*-benzyne and the Myers−Saito cyclization of hept-1,2,4-trien-6-yne to α,3-didehydrotoluene predict the activation enthalpy for the cyclization of cyclonona-1,2,3,7-tetraen-5-yne to be 17.8 kcal/mol, the exothermicity to be −1.2 kcal/mol, and the singlet−triplet splitting in the biradical to be −6.4 kcal/mol. The lower barrier and greater exothermicity in the neocarzinostatin chromophore cyclization compared to the Bergman cyclization derive, in roughly increasing magnitude of importance, from the greater stability of a transoid than a cisoid σ,σ-biradical, relief of ring strain, and differences in the nature of C−C bonds made and broken along the reaction path.

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Supporting Information Available: DFT optimized geometries for all computed structures in reactions **b** and **c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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