

Biradical and Zwitterionic Cyclizations of Oxy-Substituted Enyne-Allenenes

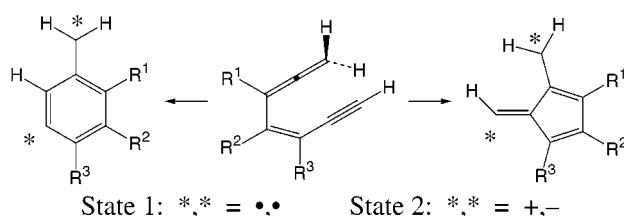
Christopher J. Cramer,* Bethany L. Kormos, Mark Seierstad,
Edward C. Sherer, and Paul Winget

Department of Chemistry and Supercomputer Institute, University of Minnesota,
207 Pleasant St. SE, Minneapolis, Minnesota 55455-0431

cramer@chem.umn.edu

Received April 4, 2001

ABSTRACT



Oxyanion substitution of enyne-allenes causes both Myers–Saito and Schmittel cyclizations to switch their product formation preferences from diradicals to polar, closed-shell singlets. The oxyanion stabilization is larger for the Schmittel products than the Myers–Saito products because the latter must sacrifice aromaticity to maximize interaction. The changing character of the different reaction paths is reflected in their activation energies.

Neocarzinostatin^{1,2} is an antitumor agent whose activity derives from its ability to undergo cycloaromatization of a 10-membered ring enyne-allene to generate a reactive 1,5-didehydroindene σ,σ -diradical while complexed to DNA. When the enyne-allene functionality is not incorporated in a ring, two different cyclization pathways have been demonstrated, as illustrated in Figure 1. The Myers–Saito^{3,4} pathway (a) is a cycloaromatization joining positions C2 and C7. This pathway is identical to that found in neocarzinostatin, except that in the absence of ring constraints the product $\alpha,3$ -didehydrotoluene is a σ,π -diradical instead of one having σ,σ character.⁵ The Schmittel⁶ pathway (c) joins positions C2 and C6 to generate a fulvene-like diradical, which also has σ,π character. Schmittel et al.^{6,7} originally demonstrated

that pathway c is energetically preferable to pathway a when the alkyne terminus C7 is substituted with sterically demanding groups.

The energetics of the two cyclizations have been studied in detail for the parent hydrocarbon hepta-1,2,4-trien-6-yne **1a**. For the Myers–Saito pathway, the best experimental values from analysis of molecular heats of formation suggests a 298 K activation enthalpy of 23.3 ± 0.5 kcal/mol³ and an enthalpy of reaction of -13.5 ± 4.0 kcal/mol.^{8,9} Gas-phase theoretical results of Engels and Hanrath at the MRCI level,¹⁰ of Cramer and Squires at the SAC–BD(T) level,⁵ and of Schreiner and Prall at the DFT and BCCD(T) level¹¹ are all in reasonably¹² good accord with experiment. The best calculations to date suggest that the activation enthalpy of the Schmittel pathway is very roughly on the order of 35 kcal/mol and it is endothermic by about 15 kcal/mol;^{10–12}

(1) Myers, A. G. *Tetrahedron Lett.* **1987**, 28, 4493.

(2) Myers, A. G.; Cohen, S. B.; Kwon, B.-M. *J. Am. Chem. Soc.* **1994**, *116*, 1670.

(3) Myers, A. G.; Kuo, E. Y.; Finney, N. S. *J. Am. Chem. Soc.* **1989**, *111*, 8057.

(4) Nagata, R.; Yamanaka, H.; Okazaki, E.; Saito, I. *Tetrahedron Lett.* **1989**, *30*, 4995.

(5) Cramer, C. J.; Squires, R. R. *Org. Lett.* **1999**, *1*, 215.

(6) Schmittel, M.; Strittmatter, M.; Kiau, S. *Tetrahedron Lett.* **1995**, *36*, 4975.

(7) Schmittel, M.; Keller, M.; Kiau, S.; Strittmatter, M. *Chem. Eur. J.* **1997**, *3*, 807.

(8) Wenthold, P. G.; Wierschke, S. G.; Nash, J. J.; Squires, R. R. *J. Am. Chem. Soc.* **1993**, *115*, 12611.

(9) Wenthold, P. G.; Wierschke, S. G.; Nash, J. J.; Squires, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 7378.

(10) Engels, B.; Hanrath, M. *J. Am. Chem. Soc.* **1998**, *120*, 6356.

(11) Schreiner, P. R.; Prall, M. *J. Am. Chem. Soc.* **1999**, *121*, 8615.

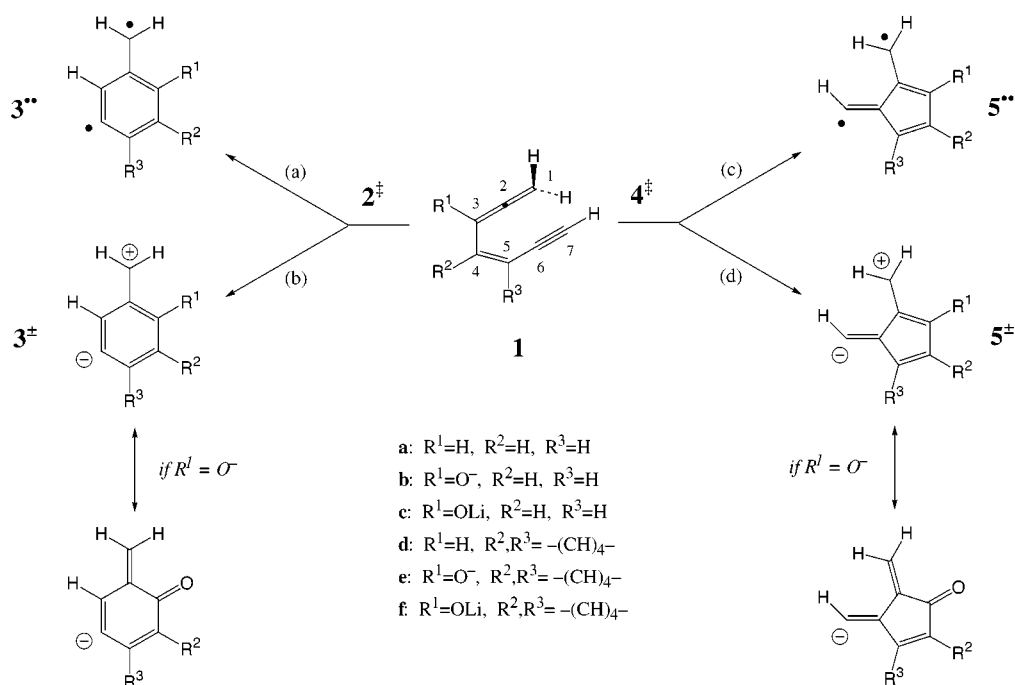


Figure 1. Electrocyclization paths for enyneallenes. The zwitterionic mesomers depicted would be expected on the basis of standard arguments to slightly dominate over the alternative polarizations, but mixing of the other mesomer into a net valence bond description in each case will make total charge separation considerably less than unity.

experimental results are not available for this path (unsurprisingly, given its significantly higher predicted activation enthalpy).

Recently, Brunette and Lipton showed that oxyanion substitution at position C3 significantly accelerates cyclization and may contribute to a preference for Schmittel-type products.¹³ We here employ density functional theory¹⁴ to quantify the changes in reaction thermochemistry associated with such a substitution (including consideration of effects associated with counterions, solvation, and benzannellation), and we rationalize the predicted changes in terms of alternative biradical and zwitterionic descriptions of the reaction paths.

Some further discussion of Figure 1 is warranted for clarity. Note that neither the Myers–Saito pathway (a) nor

the Schmittel pathway (c) is adiabatic. That is, the electronic states of the alternative product diradicals 3^{**} and 5^{**} are *different* from that for the common closed-shell reactant **1** (formally speaking, in their common C_s point group the products have electronic state symmetries that are A'' while that for **1** is A'). Pathways b and d, on the other hand, *are* adiabatic, in the sense that all electrons in products 3^\pm and 5^\pm are completely spin-paired, just as they are in **1**. Note that, since the frontier orbitals in **3** and **5** belong to different irreducible representations of their molecular point groups, in each case mixing of the diradical and zwitterionic configurations (i.e., “resonance”) is strictly forbidden, and for both **3** and **5** the “••” and “ \pm ” configurations are rigorously related to one another as different singlet states.^{25,26}

As one proceeds along either cyclization coordinate for the parent system **1a**, there comes a point at which the

(12) The interpretation of published theoretical results is somewhat complicated by prior errors. For instance, it appears that all previous computed Myers–Saito activation energies/enthalpies have been relative to the *s-cis* isomer of **1a** instead of the *s-trans*; the latter is 4 kcal/mol lower in energy and clearly dominates at equilibrium. Also, with respect to the Schmittel pathway, there is a TS structure (differing in configuration at C7) lower in energy than the one used by Schreiner and Prall.¹¹ A full discussion of these issues is not undertaken here, but we have ensured that lowest-energy structures are used in every instance (some switching takes place as a function of substitution).

(13) Brunette, S. R.; Lipton, M. A. *J. Org. Chem.* **2000**, *65*, 5114.

(14) All stationary points were optimized at the unrestricted *m*PWPW91 level^{15–17} of theory using the 6-31+G* basis set.^{18,19} This level of theory was judged to represent an optimal compromise between expected accuracy (based on comparison to experimental data) and practical applicability. Analytical frequency calculations were used to verify the natures of all stationary points and to compute thermal enthalpy contributions.²⁰ Open-shell singlet energies were computed using the sum method.^{21–23} Solvation free energies in toluene were computed at the corresponding SM5.42R level.²⁴

(15) Perdew, J. P.; Wang, Y. *Phys. Rev. B* **1986**, *33*, 8800.

(16) Perdew, J. P.; Burke, K.; Wang, Y. *Phys. Rev. B* **1996**, *54*, 16533.

(17) Adamo, C.; Barone, V. *J. Chem. Phys.* **1998**, *108*, 664.

(18) Hariharan, P. C.; Pople, J. A. *Chem. Phys. Lett.* **1972**, *66*, 217.

(19) Frisch, M. J.; Pople, J. A.; Binkley, J. S. *J. Chem. Phys.* **1984**, *80*, 3265.

(20) Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.

(21) Ziegler, T.; Rauk, A.; Baerends, E. J. *Theor. Chim. Acta* **1977**, *43*, 261.

(22) Yamaguchi, K.; Jensen, F.; Dorigo, A.; Houk, K. N. *Chem. Phys. Lett.* **1988**, *149*, 537.

(23) Cramer, C. J.; Dulles, F. J.; Giesen, D. J.; Almlöf, J. *Chem. Phys. Lett.* **1995**, *245*, 165.

(24) Li, J.; Zhu, T.; Hawkins, G. D.; Winget, P.; Liotard, D. A.; Cramer, C. J.; Truhlar, D. G. *Theor. Chem. Acc.* **1999**, *103*, 9.

(25) Salem, L.; Rowland, C. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 92.

(26) Bonacic-Koutecky, V.; Koutecky, J.; Michl, J. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 170.

originally lower energy closed-shell singlet surface crosses the open-shell diradical singlet surface owing to the higher energy associated with charge separation in the zwitterionic products **3a**[±] and **5a**[±]. The cyclization paths smoothly transition from the closed-shell surface to the open-shell one along this crossing seam so as to produce the products corresponding to the lower-energy diradical state (the actual dynamics of this surface hopping may be quite complicated,²⁷ but we will only consider the thermodynamic aspects here). All previous theoretical calculations^{5,8–11,28–31} and those reported here agree that there is no diradical character in either transition state (TS) structure **2a**[‡] or **4a**[‡], so the surface crossing seam appears to be post-activation. This is further consistent with the interpretation of competitive diradical/zwitterionic trapping experiments carried out by Myers et al. for **1a**.³²

In Table 1, we report the relative energies of all TS structures and lowest-energy singlet products relative to their respective reactants for substitution patterns **a–f**.³³ We do

Table 1. Predicted Enthalpies (H_{298} , kcal/mol) of **2–5** Relative to **1**

isomer	Myers-Saito cyclization				Schmittel cyclization			
	2 [‡]	3 ^{••}	3 [±]	t3	4 [‡]	5 ^{••}	5 [±]	t5
a	19.8 23.3±0.5 ^a	-13.0 -13.5±4 ^a	-6.1	-11.3	26.6	13.9	16.7	8.5
b	11.4		-31.6	-26.1	5.5		-27.4	-7.0
c	7.5	-25.5	-22.2	-23.9	9.7		-5.2	-3.1
d	19.2	-8.7	2.1	-7.3	24.2	8.9	19.1	8.6
e	7.4		-34.6	-28.2	1.6		-29.0	-16.1
f	6.9	-22.5	-18.8	-21.3	8.1	-7.7	-4.0	-6.9

^a Experimental data; see text.

not attempt to compute the energies of open-shell singlet products when they lie above their corresponding closed-shell singlet states; however we do report triplet (t) energies, which should in general be good indicators of open-shell singlet energies (the data in Table 1 indicate the two states to be within 2 kcal/mol of one another in six cases out of seven. Indeed, for those discomfited by a certain lack of theoretical rigor in applying Kohn–Sham DFT to open-shell singlets *at all*, one may choose simply to ignore the data in the columns headed **3**^{••} and **5**^{••}, substituting in their place

the triplet energies as an estimate—discussion below is not qualitatively affected by this choice). As for the energies of closed-shell singlets when they are not the ground state, these can be approximated by enforcing a restricted DFT determinant. Prior multireference calculations have estimated that **3a**[±] and **5a**[±] are 20–40 and 40 kcal/mol, respectively, above **3a**^{••}.^{10,31} The restricted DFT approach predicts energies for these states about 10 kcal/mol lower than previous estimates but is expected to be useful for the analysis of substitution effects irrespective of which level of theory is the more accurate in an absolute sense.

The influence of an oxyanion is made particularly clear in comparing cases **a** and **b**. For both cyclizations, the overall reaction enthalpy to generate the *triplet* state becomes more favorable by about 15 kcal/mol, reflecting the better stabilization of an oxyanion by the unsaturated rings in the diradical products than by the enyne-allene. More profound, however, is the enormous stabilization of the oxyanion when it interacts with the zwitterionic state as compared to the biradical state. By formation of an enone, the negative and positive charges of the oxyanion and zwitterion, respectively, are formally annihilated, and this causes the zwitterionic singlets **3b**[±] and **5b**[±] to be the apparent ground states in the oxyanion system. Assuming the open-shell singlet energies for **3b**^{••} and **5b**^{••} to be similar to the triplet energies (vide supra), we see that for Myers–Saito product **3b** the closed-shell state is preferred by only 5.5 kcal/mol, while for Schmittel product **5b** the preference is a much larger 20.4 kcal/mol.

Part of this apparent difference in stabilization energy derives from the loss of aromaticity in the enone mesomer of **3b**[±], a phenomenon that is not a factor in **5b**[±] (Figure 1). This can be further assessed by consideration of the benzannelated systems **d** and **e**. Wenthold and Lipton³⁴ have already noted that the reduced aromaticity of naphthalene compared to that of benzene rationalizes the smaller exothermicity of the Myers–Saito cyclization for **1d** compared to **1a** (note that the Schmittel thermochemistry is *more* favorable with benzannelation, because the π radical can be delocalized to a benzylic position). So, in **3e**[±], the cost of dearomatization to enhance enone character is reduced and the S–T splitting increases relative to system **b** by about 1 kcal/mol, i.e., the closed-shell singlet is now the ground state by an increased margin.

Insofar as the net effect of oxyanion substitution in systems **b** and **e** compared to **a** and **d** is, by large favorable interaction with the zwitterionic states, to make the Myers–Saito and Schmittel cyclizations, respectively, about 22 and 38 kcal/mol more exothermic than for the parent systems, it is unsurprising that the corresponding activation enthalpies are decreased by about 10 and 22 kcal/mol, respectively. The larger fraction of the change in overall exothermicity reflected in the change in activation enthalpy for the Schmittel process (58%) compared to that for the Myers–Saito (45%) derives from the later transition state for the former, which is endothermic in systems **a** and **d**, compared to the latter, which is exothermic. The substantial difference

(27) Bernardi, F.; Olivucci, M.; Robb, M. A. *Acc. Chem. Res.* **1990**, *23*, 405.

(28) Koga, N.; Morokuma, K. *J. Am. Chem. Soc.* **1991**, *113*, 1907.

(29) Mitra, A.; Capitani, J. F. *Int. J. Quantum Chem.* **1994**, *49*, 363.

(30) Engels, B.; Lennartz, C.; Hanrath, M.; Schmittel, M.; Strittmatter, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1960.

(31) Hughes, T. S.; Carpenter, B. K. *J. Chem. Soc., Perkin Trans. 2* **1999**, 2291.

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

(33) The *m*PWPW91/cc-pVDZ level of theory does well for the known reaction enthalpies but underestimates the best measured/predicted barrier heights for system **1** by an amount roughly consistent with using a double- ζ instead of a triple- ζ basis set.¹¹ This is not a significant concern for understanding relative effects from substitution, but absolute barriers for the substituted cases would probably be more accurately predicted if our DFT values were to be corrected upward by the same amount as required for system **1**.

(34) Wenthold, P. G.; Lipton, M. A. *J. Am. Chem. Soc.* **2000**, *122*, 9265.

in oxyanion interaction energies for the two cyclization pathways is sufficient to change the preferred reaction path (in a kinetic sense, i.e., the relative energies of 2^{\ddagger} vs 4^{\ddagger}) from Myers–Saito to Schmittel cyclization both in the parent and the benzannelated cases, the latter being consistent with the experimental work of Brunette and Lipton.¹³

The effects of lithiation in systems **c** and **f** are noteworthy. By localizing a substantial fraction of the negative charge on the oxygen (in the gas phase), the increases in reaction exothermicities of naked oxyanion substituted cases (**b** and **e**) compared to unsubstituted cases (**a** and **d**) are reduced by about half. The effect of lithiation is much larger for the closed-shell singlets, since enone formation is suppressed, than for the open-shell singlets, so for the lithiated Myers–Saito cyclizations, the diradical singlets again become the ground states. In the lithiated Schmittel products, the two states appear to be quite close to one another, closed-shell being weakly preferred for **c** and open-shell for **f**. The Schmittel activation enthalpies in the lithiated systems are intermediate between those of the unsubstituted and oxyanionic systems, as expected. The Myers–Saito activation enthalpies, on the other hand, drop very slightly in the lithiated systems compared to those in the oxyanionic ones, even though the overall exothermicities are decreased. This may be attributable to a stronger, evidently stabilizing, η^4 coordination of lithium involving C1 in structures $2\mathbf{c}^{\ddagger}$ and $2\mathbf{f}^{\ddagger}$ (compared to $1\mathbf{c}$ and $1\mathbf{f}$) that counterbalances the otherwise expected increase in activation enthalpy.

When toluene solvation free energies from SM5.42R calculations are added to the stationary point enthalpies, there

is very little effect on the relative energies of these structures—typically well under 1 kcal/mol. Across the six cases studied here, there is a very weak tendency for solvation to be better for the Myers–Saito TS structures than for the corresponding Schmittel ones. While one might naively expect zwitterionic structures to be much better solvated than diradical analogs, the actual degree of charge separation in the former is sufficiently small that this does not discriminate strongly between the two states, although it is possible that in a solvent of very high polarity this effect could be somewhat larger.

The preference for Myers–Saito vs Schmittel cyclization and indeed the overall kinetics and thermodynamics for these two reactions can be manipulated by taking advantage of the sensitivity of the different product singlet states to substitution. It should be noted, however, that any modification that makes the product(s) strongly prefer to be closed-shell singlet(s) may significantly decrease their activity as reactive intermediates. This point has some relevance for drug design.

Acknowledgment. We are grateful for financial support from the National Science Foundation and high-performance computing resources made available by the Minnesota Supercomputer Institute. This work was also supported in part by the John Simon Guggenheim Foundation, the Spanish Ministry of Education and Culture, and Fundación BBV.

OL015935E