Relative Rates of Cycloaromatization of Dynemicin Azabicyclo[7.3.1]enediyne Core Structures. An Unusual Change in $\Delta S^{\ddagger}$

Philip Magnus* and Robin A. Fairhurst

Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, Texas 78712, USA

A series of dynemicin core azabicyclo[7.3.1]enediynes undergo cycloaromatization at dramatically different rates despite the fact that the distance (*r*, by X-ray diffraction) between the bonding acetylenes is practically identical (3.4 Å); when the carbamate protecting group is removed to give the *sec*-amine **10**, it cycloaromatizes more rapidly, and the entropy of activation changes from a negative to positive.

The enediyne antitumour antibiotic dynemicin **1** has generated considerable interest both in its synthesis and its *in vitro* mechanism of antitumour action.[1] We have previously shown that the dynemicin core azabicyclo[7.3.1]enediyne **2** is considerably more resistant to cycloaromatization than the corresponding esperamicin–calicheamicin core **3** despite the fact that the distance (*r*, by X-ray diffraction) between the bonding acetylenes is practically identical (3.4 Å).[2] It required heating **2** in cyclohexa-1,4-diene at 124 °C for 18 h to convert it into **4** (84%), giving an approximate $\Delta G^{\ddagger}$ = 30.9 kcal mol^{-1} (1 cal = 4.184 J), whereas the enediyne **3** conversion into **5** gave $\Delta G^{\ddagger}$ = 26.3 kcal mol^{-1} (Scheme 1).[3]

During our investigations on the synthesis and chemistry of dynemicin-like compounds we have found a series of enediynes where the bonding distance between the acetylenes (*r*) is virtually identical, but their relative rates of cycloaromatization are dramatically different.[4] Measuring the rate of cycloaromatization of **6** (*r* = 3.4 Å, X-ray) to give **7** (92%) in 3,6-dihydrotoluene from 65 to 114 °C gave the thermodynamic parameters, $\Delta G^{\ddagger}$ = 29.0 kcal mol^{-1}, $\Delta H^{\ddagger}$ = 26.1 kcal mol^{-1}, $\Delta S^{\ddagger}$ = −9.3 cal mol^{-1} K^{-1}, E_a = 26.8 kcal mol^{-1}. The data was extrapolated to 37 °C (Scheme 2), and clearly shows that **6** is stable under physiological conditions.

There is a modest solvent effect on the rate of cyclization of **6** to **7**, $t_{1/2}$ (cyclohexadiene 81 °C) = 10.9 h *vs.* $t_{1/2}$ (3,6-dihydrotoluene 81 °C) = 35.0 h, $t_{1/2}$ (THF, 67 °C) = 114.9 h *vs.* $t_{1/2}$ (3,6-dihydrotoluene, 67 °C) 167.4 h.

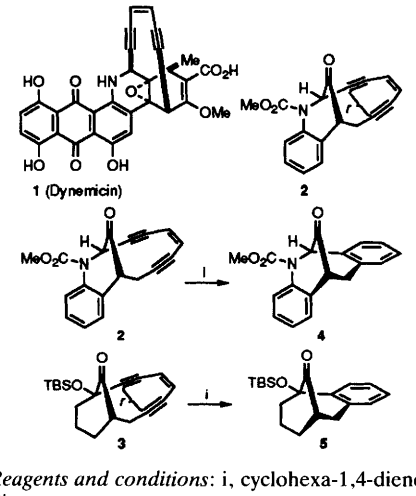
Treatment of **6** with LiN(SiMe$_3$)$_2$–THF–ClCH$_2$OMe at −78 °C gave **8** (81%), which upon cycloaromatization to **9** (>95%), as above, gave the parameters, $\Delta G^{\ddagger}$ = 30.16 kcal mol^{-1}, $\Delta H^{\ddagger}$ = 26.11 kcal mol^{-1}, $\Delta S^{\ddagger}$ = 9.3 cal mol^{-1} K^{-1}, E_a = 33.0 kcal mol^{-1}, $t_{1/2}$ (37 °C) = 6.28 yr.

The amine **10** (formed by treatment of **6** with CF_3CO_2H) was heated in THF at temperatures from 51 to 67 °C (to give **11**) and gave from an Arrhenius plot $\Delta G^{\ddagger}$ = 28.1 kcal mol^{-1}, $\Delta H^{\ddagger}$ = 36.9 kcal mol^{-1}, $\Delta S^{\ddagger}$ = +28.3 cal mol^{-1} K^{-1}, E_a = 37.6 kcal mol^{-1} (Scheme 1). The most notable feature is that the rate of cycloaromatization of the *sec*-amine increases more rapidly with increasing temperature than the carbamates **6** and **8**. At 37 °C, **10** cycloaromatizes 1.6 times faster than **6**, and at 65 °C the difference increases to 20 times ($\Delta G^{\ddagger}$ = 29 and 28.1 respectively). The origin of this difference lies in the $T\Delta S^{\ddagger}$ term.

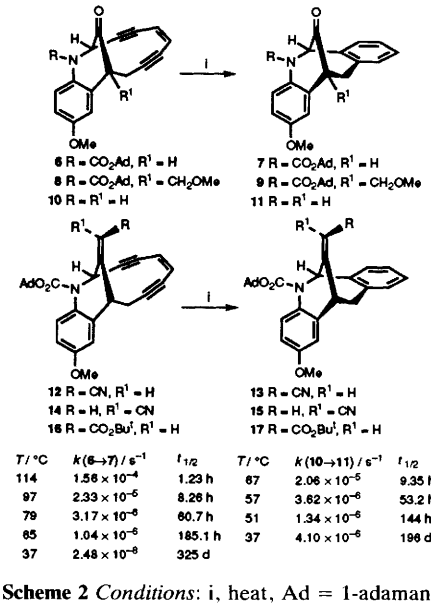
The remarkable change in entropy (**10**, $\Delta S^{\ddagger}$ = +28.3 cal mol^{-1}; **6**, $\Delta S^{\ddagger}$ = −9.3 cal mol^{-1}) appears to be caused by hydrogen bonding. Both the NH and C=O infrared bands of **10** change as a function of concentration, indicating intermolecular hydrogen bonding. Variable-concentration ^{1}H NMR also confirmed this phenomenon. The degree of intermolecular hydrogen bonding (aggregation) is a function of temperature, and therefore causes the entropy of activation to increase and become positive (dissociation).[5]

The ketone **6** reacted with (EtO)$_2$P(O)CH$_2$CN–Bu^{n}Li at 0 °C to give **12** (80%) as a single stereoisomer. Treatment of **12** with LiN(SiMe$_3$)$_2$–THF at −78 °C followed by protonation gave a separable mixture of **12** and **14** (1:1). These two compounds were readily cycloaromatized to give **13** and **15** respectively. For **12** into **13**, $\Delta G^{\ddagger}$ = 25.1 kcal mol^{-1}, $\Delta H^{\ddagger}$ = 21.7 kcal mol^{-1}, $\Delta S^{\ddagger}$ = 10.9 cal mol^{-1} K^{-1}, E_a = 22.2 kcal mol^{-1}, $t_{1/2}$ (37 °C) = 15.3 h. For **14** into **15** $t_{1/2}$ (37 °C) = 15.0 h. Likewise the α,β-unsaturated ester **16** cyclized to give **17**, $t_{1/2}$ (22 °C) = 54.4 h, *vs.* **12**, $t_{1/2}$ (22 °C) = 90.4 h.

While the distance (*r*) between the bonding acetylenic carbon atoms in **6** and **12** is virtually the same, and the hybridization at the bridging carbon atom is trigonal in both compounds, **12** cycloaromatizes *500 times* faster than **6** at 37 °C! An even more dramatic change in rate occurs when the bridging trigonal carbon atom is made tetrahedral. Reduction of **6** with sodium borohydride in methanol at 25 °C gave directly the cycloaromatized alcohol **19** (37%) (Scheme 3). We could not detect the intermediate enediyne **18**. Using a conservative estimate, the alcohol **18** cycloaromatizes *10^6 faster* than **6** at 37 °C! The stereochemistry of **18** results from



Scheme 1 *Reagents and conditions*: i, cyclohexa-1,4-diene, heat, TBS = Bu^{t}Me$_2$Si



T/°C	k(6→7)/s^{-1}	$t_{1/2}$	T/°C	k(10→11)/s^{-1}	$t_{1/2}$
114	1.56 × 10^{-4}	1.23 h	67	2.06 × 10^{-5}	9.35 h
97	2.33 × 10^{-5}	8.26 h	57	3.62 × 10^{-6}	53.2 h
79	3.17 × 10^{-6}	60.7 h	51	1.34 × 10^{-6}	144 h
65	1.04 × 10^{-6}	185.1 h	37	4.10 × 10^{-6}	196 d
37	2.48 × 10^{-8}	325 d			

Scheme 2 *Conditions*: i, heat, Ad = 1-adamantyl

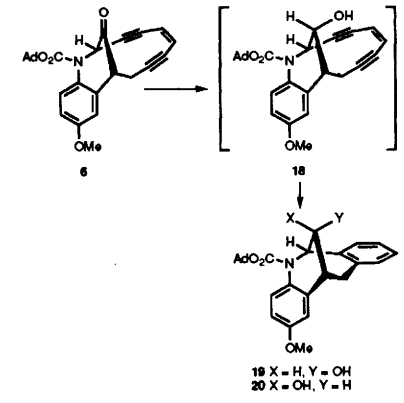
hydride approach from the least-hindered face opposite the enediyne. Reduction of **7** under the same conditions gave a mixture of **19** (56%) and **20** (26%).

While all of the above cycloaromatization rate studies were conducted with the exclusion of air (oxygen), for the slower reactions, for example **6** into **7** at 65 °C, it was found that a new product slowly accumulated as air was leaked into the reaction mixture (only observed in cyclohexa-1,4-diene, not in THF). The new compound turned out to be the cycloaromatized lactone **21** (Scheme 4), and an authentic sample was made by treating **7** with *m*-chloroperoxybenzoic acid (MCPBA). Surprisingly, when **6** was exposed to MCPBA the amideacetal **23** (80%) was the only isolable product. Even if less than 1 equivalent of oxidant was used, **23** and **6** were the only materials present.[6] Apparently, the further Baeyer–Villiger oxidation of the presumed intermediate **22** (in the open iminium ion form) is faster than **6**! When **23** was heated at 140 °C the enediyne extruded carbon dioxide, cycloaromatized and further eliminated water to give the indole derivative **24** (15%).

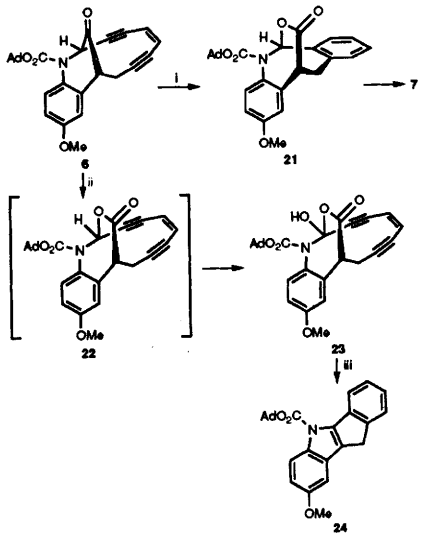
Quantitative investigations led us to propose that an overall change in strain energy from enediyne to cycloaromatized adduct furnishes the closure driving force. More recently, we presented computational evidence that factors controlling the ease of cycloaromatization are directly related to strain energy in the transition state rather than to proximity of the acetylenic carbon atoms (*r*) in the ground state.[2] The quantitative experimental data reported above support the strain hypothesis, but the relative rates are not predicted by computational methods that worked in the esperamicin–calicheamicin core compound(s) **3**. It therefore appears that the small changes in $\Delta G^{\ddagger}$, that are manifested in substantial rate differences, are difficult to match by computational methods.

The National Science Foundation, National Institutes of Health and Bristol–Myers Squibb are thanked for their support of this research. Dr David Langley (Bristol–Myers Squibb) is thanked for his efforts to match the relative values of $\Delta G^{\ddagger}$ by computational methods.

Received, 15th March 1994; Com. 4/01558D



Scheme 3



Scheme 4 *Reagents and conditions*: i, heat, air; ii, MCPBA; iii, 140 °C, 48 h

References

1 M. Konishi, H. Ohkuma, K. Matsumoto, T. Tsuno, H. Kamei, T. Miyaki, T. Oki, H. Kawaguchi, G. D. Van Duyne and J. Clardy, *J. Antibiot.*, 1989, **42**, 1449; M. Konishi, H. Ohkuma, T. Tsuno, T. Oki, G. D. Van Duyne and J. Clardy, *J. Am. Chem. Soc.*, 1990, **112**, 3715; molecular modelling of the dynemicin–DNA complex predicts the absolute configuration to be 2*S*, 3*S*, 4*S*, 7*R*, 8*R*, D. R. Langley, T. W. Doyle and D. L. Beveridge, *J. Am. Chem. Soc.*, 1991, **113**, 4395. Synthetic studies, see: J. A. Porco, Jr, F. J. Schoenen, T. J. Stout, J. Clardy and S. L. Schreiber, *J. Am. Chem. Soc.*, 1990, **112**, 7410. J. L. Wood, J. A. Porco, Jr., J. Taunton, A. Y. Lee, J. Clardy and S. L. Schreiber, *J. Am. Chem. Soc.*, 1992, **114**, 5898; J. Taunton, J. L. Wood and S. L. Schreiber, *J. Am. Chem. Soc.*, 1993, **115**, 1037; K. C. Nicolaou, C.-K. Hwang, A. L. Smith and S. V. Wendeborn, *J. Am. Chem. Soc.*, 1990, **112**, 7416. K. C. Nicolaou, A. L. Smith, C.-K. Hwang and S. V. Wendeborn, *J. Am. Chem. Soc.*, 1991, **113**, 3114; P. A. Wender and C. K. Zercher, *J. Am. Chem. Soc.*, 1991, **113**, 2311; K. C. Nicolaou and W.-M. Dai, *Angew. Chem., Int. Ed. Engl.*, 1991, 1387; K. C. Nicolaou, C. W. Hummel, E. N. Pitsinos, M. Nakada, A. L. Smith, K. Shibayama and H. Saimoto, *J. Am. Chem. Soc.*, 1992, **114**, 10082.

2 P. Magnus, P. Carter, J. Elliott, R. Lewis, J. Harling, T. Pitterna, W. E. Bauta and S. M. Fortt, *J. Am. Chem. Soc.*, 1992, **114**, 2544.

3 For the η^2-$Co_2(CO)_6$-mediated approach, see: P Magnus and S. M. Fortt, *J. Chem. Soc., Chem. Commun.*, 1991, 544.

4 For calculations concerning the rate of diyl formation, see: J. P. Snyder and G. E. Tipword, *J. Am. Chem. Soc.*, 1990, **112**, 4040 3; J. P. Snyder, *J. Am. Chem. Soc.*, 1989, **111**, 7630; J. P. Snyder, *J. Am. Chem. Soc.*, 1990, **112**, 5367; molecular strain rather than π-bond proximity determines the cycloaromatization rates of bicyclo-[7.3.1]tridecadiynenes, P. Magnus, S. M. Fortt, T. Pitterna and J. P. Snyder, *J. Am. Chem. Soc.*, 1990, **112**, 4986; M. F. Semmelhack, J. Gallagher and D. Cohen, *Tetrahedron Lett.*, 1990, **31**, 1521; M. F. Semmelhack, J. Gallagher, T. Minami and T. Date, *J. Am. Chem. Soc.*, 1993, **115**, 11618. We have recently discovered a thiol-induced pathway that leads to a different aromatization product, and does not involve a 1,4-diradical, P. Magnus and S. A. Eisenbeis, *J. Am. Chem. Soc.*, 1993, **115**, 12627.

5 N. S. Isaacs, *Physical Organic Chemistry*, Longman Scientific & Technical, London, 1987.

6 The so-called double Baeyer–Villiger oxidation of diethyl ketals gives a mixture of orthocarbonates and carbonate, W. F. Bailey and M.-J. Shih, *J. Am. Chem. Soc.*, 1982, **104**, 1769.