Tetrahedron Letters, Vol.31, No.11, pp 1521-1522, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

BIOREDUCTIVE ALKYLATION AS A TRIGGER FOR TOXIC EFFECTS OF DYNEMICIN

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Summary. The endiyne derivative, dynemicin, is postulated to undergo bioreductive cis ring opening of a benzylic epoxide and activate the endiyne unit for Bergman rearrangement to an arene-1,4-diyl.

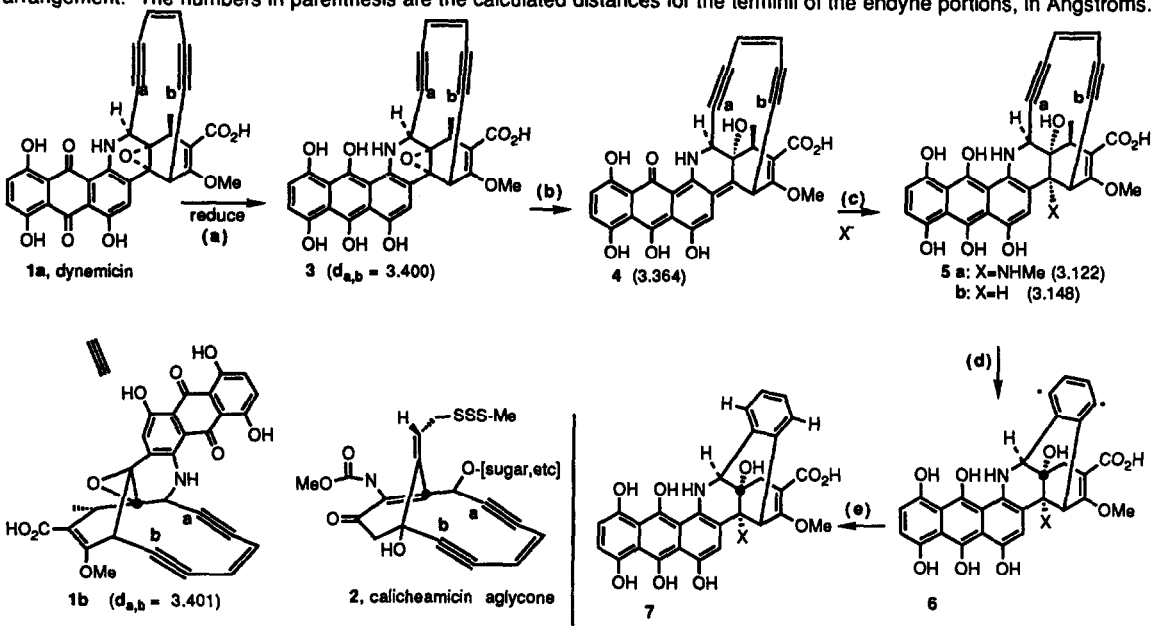
The endiyne class of antibiotics continues to grow with the addition of dynemicin (**1**)[1] to the list which includes calicheamicin (**2**), the closely related esperamicin, and neocarzinostatin.[2] For **2** (and esperamicin), the toxicity is attributed to remarkable activation steps: (a) association with DNA, (b) reductive cleavage of the trisulfide, (c) intramolecular addition of thiol, (d) thermal cyclization of the endiyne moiety to an arene-1,4-diradical, and (d) H-atom abstraction from the DNA causing strand breaking. Steps (b) and (c) constitute a "trigger" which changes the structure in a way to facilitate rearrangement to the high energy diradical.[2] It is proposed that the endyne must be poised with the proper distance ($d_{a,b}$ in **1b** and **2**) between the alkyne terminii: >3.3-3.4 Å provides a barrier which prohibits fast rearrangement at 37°C while a distance of <3.1-3.2 Å makes endiynes of this type impossible to isolate at room temperature.[3] The change predicted to be responsible for activation of **2** is calculated to be from 3.35 Å to 3.16 Å.[3]

Dynemicin (**1**) is an anti-tumor and antibacterial agent.[1] While there is no evidence nor speculation reported for the mechanism of action of (**1**), the obvious structural similarity (**1b**) with calicheamicin (**2**) prompts consideration of a parallel mechanism of toxic effects. The key structural change in **2** is the geometry change (sp^2 to sp^3) at the carbon with a heavy dot. Ring opening of the epoxide in **1** might provide a similar change although due to structural restraints, the opening must be cis. A well established mechanism for activation of quinone derivatives as alkylating agents is "bio-reduction" and elimination of a benyzlic heteroatom to give an ortho-quinomethide.[4] Applied to dynemicin, the reduction (step **a** in Scheme 1) would lead to an anthracene (**3**) which can favor epoxide ring opening (step **b**) to the ortho-quinomethide, **4**. Then addition (cis) by a nucleophile (e.g., an amino group[5]) regenerates an anthracene as in **5**. If the change in geometry is sufficient, endiyne rearrangement to the diradical **6** would be fast, and the arene **7** would result after H-atom abstraction.

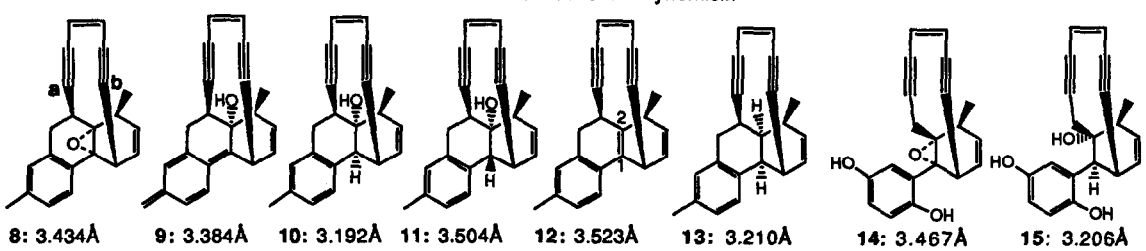
We have carried out molecular mechanics calculations[6] on **1** and hypothetical species **3**, **4**, **5**, and **7**. The parameter of interest is the distance between the alkyne terminii ($d_{a,b}$, shown with each structure). While **1** and the early intermediates **3** and **4** show bond distances above 3.35 Å, amine addition (to give **5a**) shortens the distance to 3.12 Å. A similar shortening is observed if the nucleophile is H^- (**5b**).

Simpler models (Scheme 2) focus on epoxide ring opening as a geometry perturbation responsible for triggering endiyne rearrangement. The sequence **8-9-10** again shows the relevant geometry changes, ignoring heteroatoms other than the epoxide oxygen. Bioreductive alkylation also provides a direct route to <u>cis</u> opening of the epoxide. Comparison of **10** and **11** shows that <u>trans</u> opening of the epoxide would increase slightly $d_{a,b}$. The conversion **12-13** suggests that saturation of a double bond (C_1-C_2) provides a geometry change comparable to ring opening of the epoxide. Comparison of the conversion **14-15** with **8-10** suggests that the central ring hexahydrophenanthrene unit (and, by implication, the piperidine ring in **1**) is not crucial to the geometry change. The ring opening of **14** (through an implied o-quinomethide and addition of H^-) gives a slightly greater change in $d_{a,b}$ compared to **8** and **1**. The special triggering mechanism for dynemicin (**1**) and the simple models suggest a group of new DNA cleaving agents with an electron transfer reductive initiation.[7]

Scheme 1. Relationship of dynemicin to calicheamicin; proposed intermediates in the reductive triggering and endyne rearrangement. The numbers in parenthesis are the calculated distances for the terminii of the endyne portions, in Ångstroms.



Scheme 2. Models Based on Dynemicin



References

1. (a) Konishi, M.; Ohkuma, H.; Matsumoto, K.; Tsuno, T.; Kamei, H.; Miyaki, T.; Oki, T.; Kawaguchi, H. and Clardy, J. poster presented at the 29th Intersci. Conf. on Antimicrobial Agents and Chemotherapy, Houston, TX September, 1989. (b) Konishi, M.; Ohkuma, H.; Matsumoto, K.; Tsuno, T.; Kamei, H.; Miyaki, T.; Oki, T.; Kawaguchi, H.; Van Duyne, G. and Clardy, J. *J. Antibiotics*, **1989**, *92*, 1449.

2. For a recent computational analysis and background references, see: (a). Snyder, J. P. *J. Am. Chem. Soc.*, **1989**, *111*, 7630. (b). For leading references and a discussion of a model for calcheamicin/esperamicin obtained by synthesis including an internal trigger, see: Haseltine, J. N.; Danishefsky, S. J. and Schulte, G. *J. Am. Chem. Soc.*, **1989**, *111*, 7638.

3. The concept that the rate of endiyne cyclization will depend on the distance between the alkyne terminii was presented by Dr. Robert Babine at 13th Cyanamid Synthesis Workshop at Princeton, NJ, May 22, 1987. (a). The hypothesis has been summarized and tested in monocyclic models: Nicolaou, K. C.; Zuccarello, G.; Ogawa, Y.; Schweiger, E. J. and Kumazawa, T. *J. Am. Chem. Soc.*, **1988**, *110*, 4866. (b). Bicyclic models with X-ray structural data have been discussed: Magnus, P.; Lewis, R. T. and Huffman, J. C. *J. Am. Chem. Soc.*, **1988**, *110*, 6921. It has been pointed out that in more complex polycyclic ring systems, the bond distance **a-b** is not the only factor influencing the rate of diradical formation.[2a]

4. For a review, see: Moore, H. W. and Czerniak, R. *Medicinal Res. Rev.*, **1981**, *1*, 249.

5. The 2-amino group of 2'-deoxyguanosine is one of the nucleophiles involved in anthracycline bio-reductive activation. See: Egholm, M. and Koch, T. H. *J. Am. Chem. Soc.*, **1989**, *111*, 8291.

6. Molecular mechanics calculations were carried out on MacroModel Version 2.5, copywrite 1989 Columbia University. The MM2 forcefield and FMNR geometry optimization routine were used to find the lowest energy conformers. We thank Professor Clark Still for supplying the program.

7. This work was supported by a grant under the American Cyanamid Grant Program at Princeton University.

(Received in USA 4 December 1989)