# Chemistry and biology of the calicheamicins


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The chemical reaction shown in Fig. 1a appears to be thermally allowed. Sondheimer may have stumbled on it in 1966 [1], Masamune observed its products in 1971 [2], and Bergman, after whom it is now named, demonstrated it in the laboratory in 1972 [3]. This reaction is the basis of the mechanism of action of an amazing class of molecules — some natural, some discovered by molecular design and chemical synthesis — which induce biochemical transformations that cause cell death. This new class of bioactive compounds, known as the enediynes [4,5], are exemplified by the naturally occurring calicheamicin $\gamma_1^I$ [Fig. 1b (1)] and its designed mimic, calicheamicin $\theta_1^I$ [Fig. 1b (2)], whose fascinating story is still unfolding. The calicheamicin $\gamma_1^I$ story [6] began with chalky rocks (caliche in Greek) collected near a Texas highway by a touring scientist. These rocks harbored bacteria *(Micromonospora echinospora ssp calichensis)* that in culture produced calicheamicin $\gamma_1^I$ and several related compounds. The phenomenal potencies of these new substances ($IC_{50}$ ~$10^{-12}$ M) against tumor cells provided the impetus for their structural elucidation.

Calicheamicin $\gamma_1^I$ is a masterpiece of molecular design, which undoubtedly required millions of years of evolution to reach its present state of sophistication. Its elegant mechanism of action (Fig. 1c) begins with a nucleophilic attack on the trisulfide moiety, which acts as a triggering device. The internal sulfur nucleophile thus generated undergoes conjugate addition to the enone. Bergman cycloaromatization then forms a highly reactive 1,4-benzenoid diradical which attacks DNA, causing double-strand cuts and eventual cell death.

The enediyne moiety in calicheamicin $\gamma_1^I$ would have had a low energy of activation for the Bergman reaction, because it is within a 10-membered ring; but the compound is generally stable, because the double bond in the enone acts as a lock or safety catch. The trisulfide triggering device, in the proper orientation, provides the means for undoing the lock. The oligosaccharide moiety serves as a delivery system by binding to DNA; its affinity for DNA is enhanced by the iodine atom included in the 6-membered aromatic ring. Thus, calicheamicin $\gamma_1^I$ is a highly advanced and efficient molecular device for seeking and damaging its target, DNA.

The magnificent structure and potential clinical importance of calicheamicin stimulated many groups to initiate projects ranging from total synthesis to molecular design, from computational chemistry to molecular recognition, and from DNA scission to cancer chemotherapy. In our laboratories, we have accomplished the total synthesis of the natural product [7] as well as the design and synthesis of a series of biological mimics, including calicheamicin $\theta_1^I$. On the way we were rewarded with several new findings in the areas of synthetic strategies and technology.

In molecular structure, the natural (1) and designed (2) calicheamicins differ only with respect to the triggering device; the former contains a trisulfide unit and requires a strong nucleophile for activation, the latter contains a thioacetate group and requires only a mildly basic environment to initiate the cascade of reactions leading to DNA damage (Fig. 1c). Subsequent to the triggering event, their mechanism of action is identical. The DNA-binding activity and sequence specificity of the two molecules is virtually identical; the designed molecule cleaves DNA at the TCCT site with higher potency, particularly under basic conditions (Fig. 1d) [8]. Calicheamicin $\theta_1^I$ (2) is also more potent in its ability to initiate apoptosis (Fig. 1e), or programmed cell death. Currently the focus of much interest in biology, this process is crucial in cell differentiation, immunoregulation, oncogenesis, neuronal development, and AIDS. Although the precise mechanism by which enediynes induce apoptosis is not known, their ability to cause double-stranded DNA cleavage is most likely to be responsible for this action. It is a credit to the power of synthetic organic chemistry that molecules such as the calicheamicins can be made available for further biological investigations.

**References**


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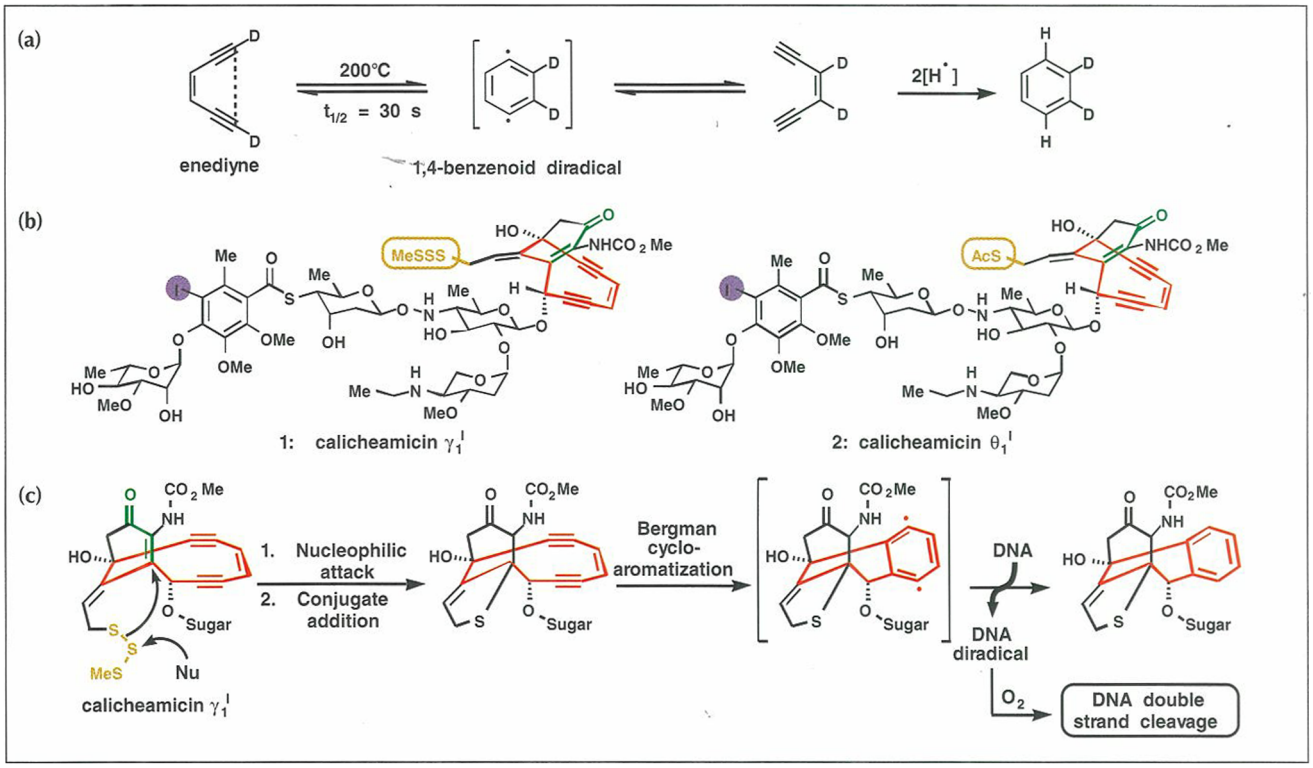


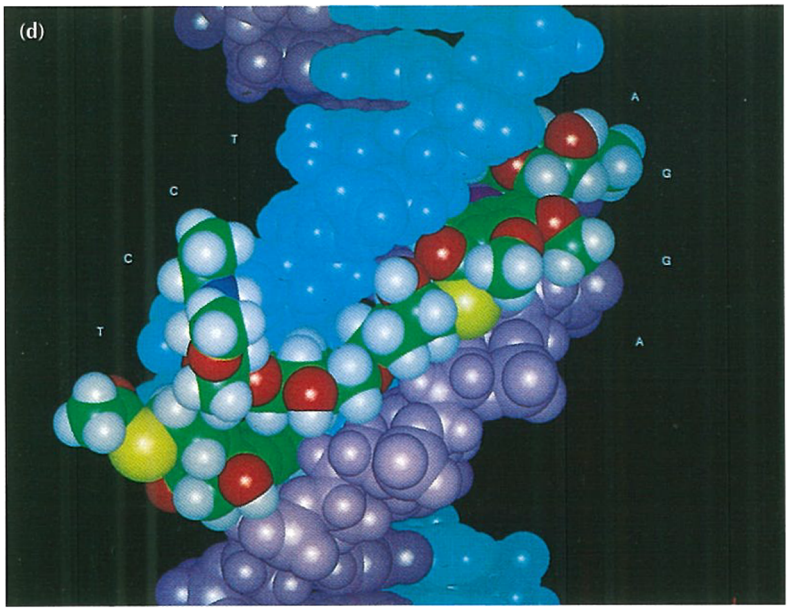


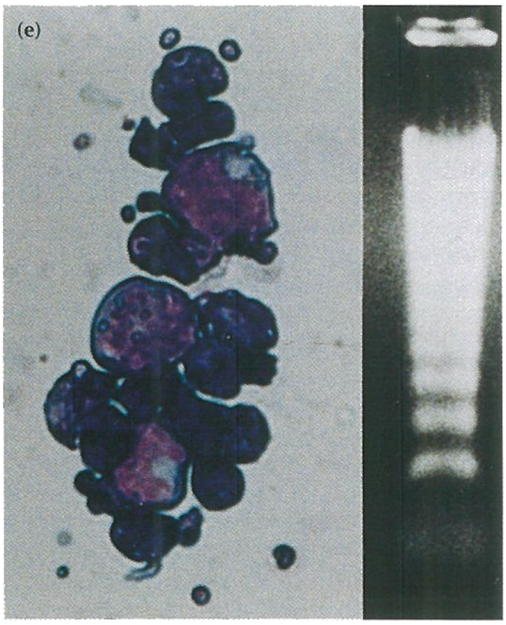


**Fig. 1.** **(a)** The Bergman cycloaromatization reaction. **(b)** Molecular structures of calicheamicin $\gamma_1^I$ (1, natural) and $\theta_1^I$ (2, designed). Both molecules consist of a 10-membered ring (red), an enone functionality (green) in a 6-membered ring and a tetrasaccharide moiety interrupted by a 6-membered aromatic ring, which contains an iodine atom (purple). Notice that the triggering device (yellow) is a trisulfide unit for calicheamicin $\gamma_1^I$ and a thioacetate group for calicheamicin $\theta_1^I$. **(c)** The mechanism of action of calicheamicin $\gamma_1^I$. **(d)** Computer generated molecular model showing minor groove binding of calicheamicin $\theta_1^I$ to double-stranded DNA along a TCCT site. **(e)** Apototic morphology and characteristic DNA ladder of Molt-4 leukemia cells obtained after exposure to calicheamicin $\theta_1^I$ (reprinted by permission from [8]).