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DIRECT OBSERVATION OF ESR SPECTRA OF BICYCLIC NINE-MEMBERED ENEDIYNES AT AMBIENT TEMPERATURE[‡]

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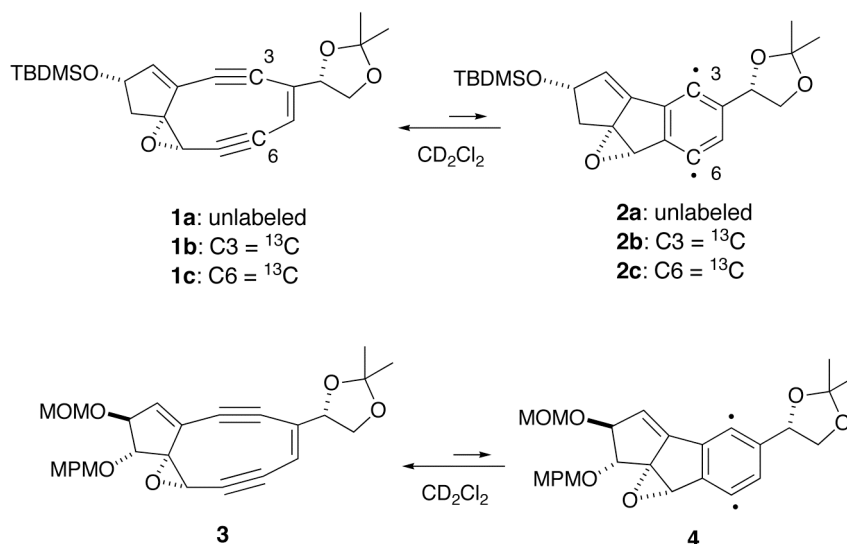
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Abstract – The ESR spectra for synthetic bicyclo[7.3.0]epoxydodecadienediynes in solution at room temperature are steady. These spectra originate from the Masamune-Bergman cyclization of bicyclo[7.3.0]epoxydodecadienediynes to *p*-benzyne biradicals and the equilibrium between the two forms. Comparison of the ESR spectra of the unlabeled and ¹³C-labeled nine-membered enediynes indicated that the spectra are not directly due to the *p*-benzyne biradicals but rather to more stable secondary radical intermediates.

The enediyne class of potent antitumor antibiotic natural products has posed chemical and biological challenges.¹⁻⁵ One elusive issue in enediyne chemistry has been the direct ESR observation of 1,4-didehydrobenzene (*p*-benzyne biradical) intermediates generated by the Masamune-Bergman cyclization of enediynes.⁶⁻¹⁰ Most theoretical^{5,11} and photoelectron spectroscopic studies¹² have suggested that the *p*-benzyne would have a singlet ground state; however, an *ab initio* calculation suggested that the singlet-triplet energy splitting (ΔE_{ST}) of *p*-benzynes is highly susceptible to and can be greatly reduced by structural perturbation.¹³ For instance, ΔE_{ST} calculated for even a simple *p*-benzyne, 2,3-dimethyl-*p*-benzyne, is 0.6 kcal/mol, whereas the value is 3.8 kcal/mol for nonsubstituted *p*-benzyne.

[‡]Dedicated to Professor Satoshi Omura on the occasion of the 70th birthday

In other words, the singlet and triplet states are almost degenerate in such a system. Therefore, it is possible that the Boltzman distribution of the triplet state of **2** at ambient temperature might be sufficient to allow its detection by ESR spectroscopy. The epoxyenediynes core model (**1**)⁶ of the kedarcidin chromophore⁷ as well as **3**¹⁴ has significantly perturbed and complex structure, and is known to be in equilibrium with *p*-benzyne (**2**) at ambient temperature.^{6,7} Our recent studies using spin trapping of isotopomers¹⁵ of **1** with ¹³C labels at the radical-forming positions C3 and C6 supported the intermediacy of **2** in the spontaneous cycloaromatization of **1** at ambient temperature.⁹ Furthermore, the recent publication¹⁶ of *in situ* ESR spectroscopy of aromatic diyne cyclopolymerization prompted us to describe the ESR spectra of **1** and **3**.



Scheme 1. Spontaneous thermal Masamune-Bergman cyclization of the nine-membered ring of bicyclic enediynes (**1** and **3**) to form *p*-benzyne biradicals (**2** and **4**, respectively).

MPM: *p*-methoxyphenoxyethyl.

We first recognized in 1995 the paramagnetic activity of **1a** in conjunction with its spontaneous equilibration with *p*-benzyne (**2a**) in solution.⁶ Figure 1A shows the X-band continuous wave (CW) ESR spectrum obtained for a 40 mM deoxygenated CD₂Cl₂ solution of **1a** in a quartz tube at ambient temperatures after careful chromatographic purification. Identical steady spectra were also observed in CH₂Cl₂ and CD₃CN at the same temperatures. These results demonstrated that the detected radical species did not arise from the solvents. Surprisingly, the spectrum (Figure 1A) was observed even after the deoxygenated CD₂Cl₂ solution was stored for 2 years at -20° C. The half-life of the spectrum was approximately 11 h in the presence of air at ambient temperature. Another synthetic enediynes (**3**)¹⁴ exhibited an ESR spectrum similar to that of **1a** in a degassed CD₂Cl₂ solution (Figure 2). The *g* values, 2.0023 and 2.0022 for **1a** and **3**, respectively, confirmed that the radical spectra were carbon-centered.

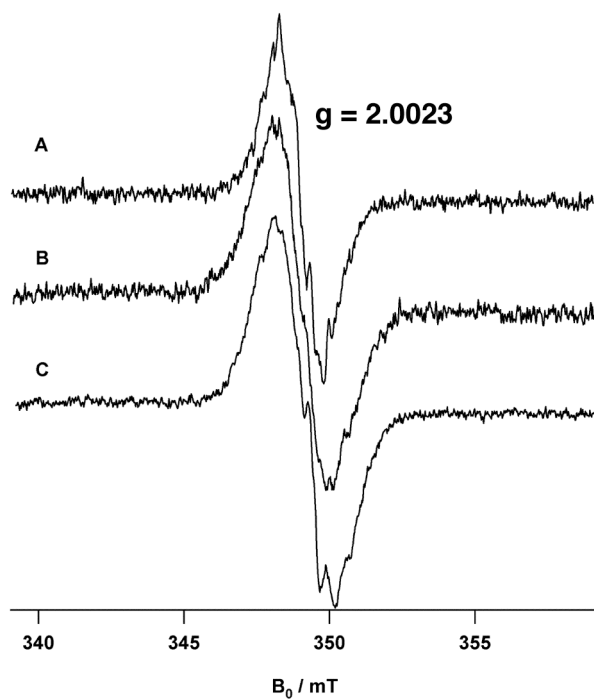


Figure 1. CW ESR spectra of enediynes **1** in CD_2Cl_2 at $25\text{ }^\circ\text{C}$. (A) unlabeled enediyne (**1a**). (B) ^{13}C -labeled enediyne (**1b**). (C) ^{13}C -labeled enediyne (**1c**).

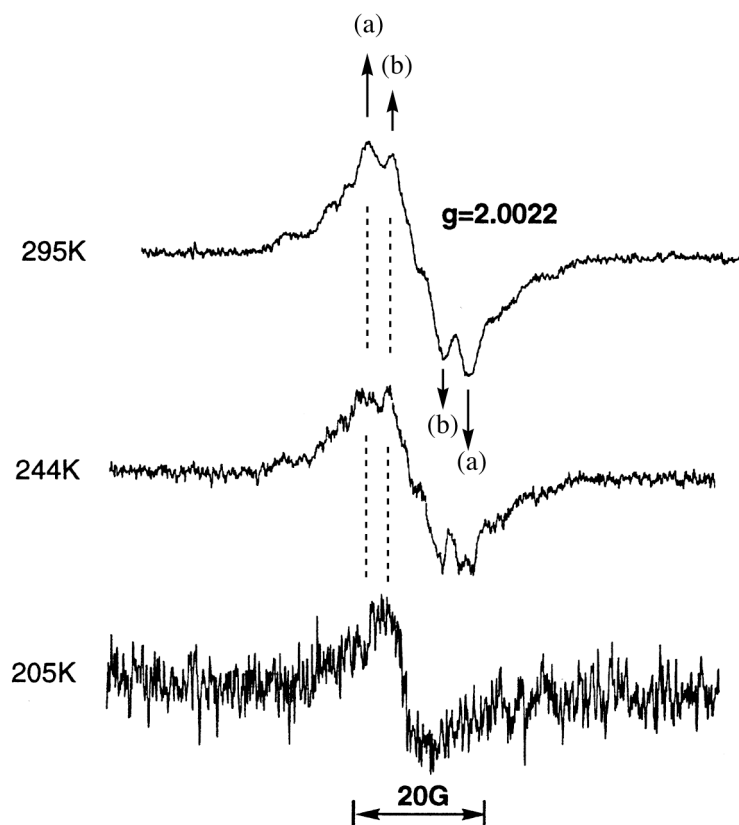


Figure 2. CW ESR spectra of enediyne (**3**) in CD_2Cl_2 at various temperatures.

Both EPR spectra showed very similar temperature dependencies. As illustrated in Figure 2, the intensities of the outer part (a) of the ESR spectra undergo larger changes than inner part (b), suggesting the existence of at least two different carbon-radical species. No signal corresponding to $\Delta m_s = \pm 2$ was observed even at 20 K. Furthermore, the pulsed two-dimensional electron spin echo transient nutation ESR technique¹⁷ indicated the presence of only mono-radicals at 6.5 MHz ($S=1/2$) and the absence of triplet ($S=1$) biradicals at 260 and 303 K (Figure 3).⁷ On the other hand, the NMR and MALDI-TOFMS analyses showed neither detectable monomeric products nor even polymeric products but instead the presence of only **1a**, irrespective of the presence of air, indicating the presence of a very small quantity of radical species existed as expected from the extremely low equilibrium constant of the process supplying **2a**.^{6,9}

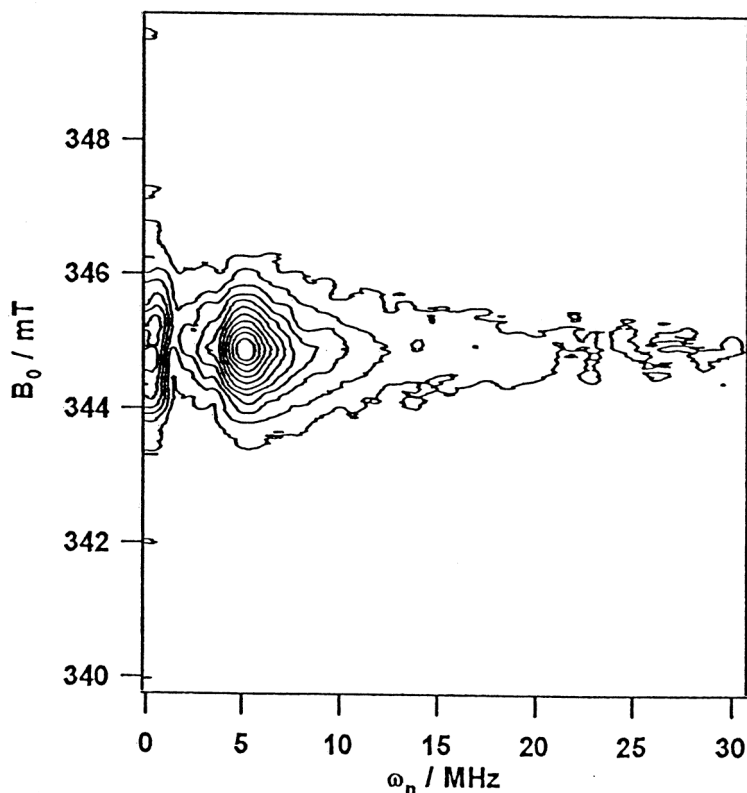
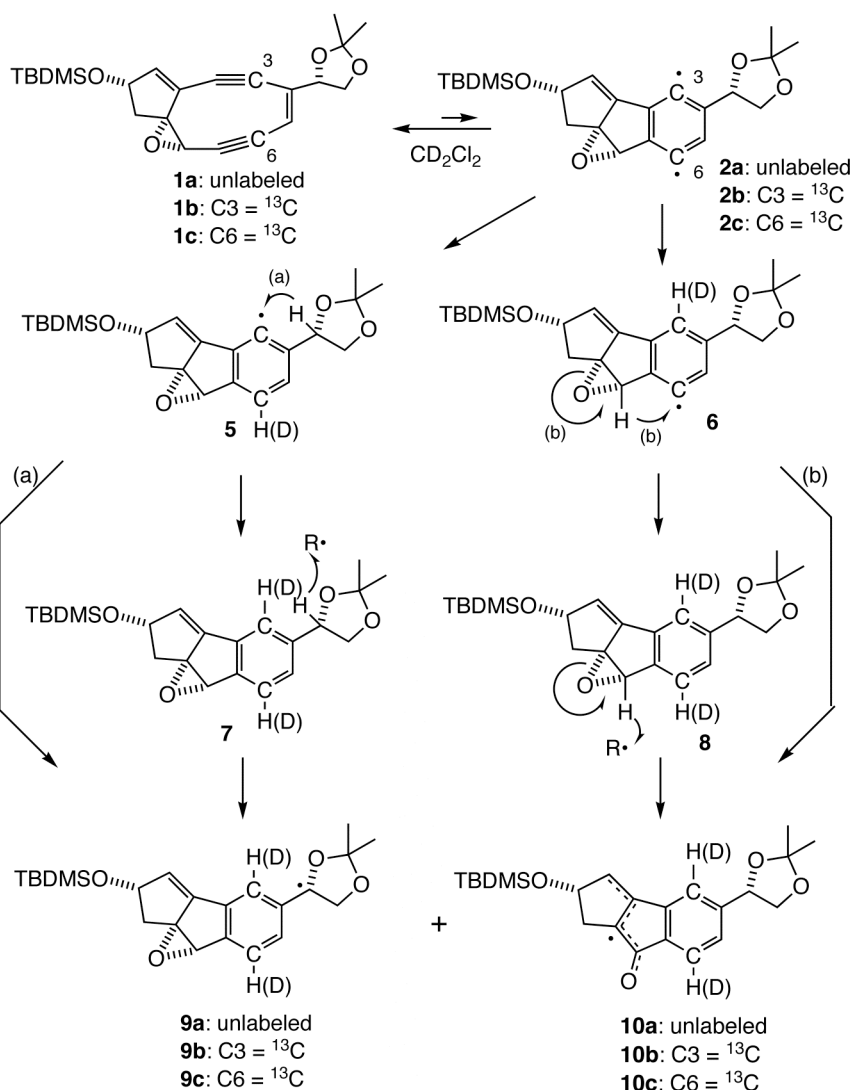


Figure 3. Pulsed two-dimensional electron spin echo transient nutation spectrum (contour plot) of **1a** at 303 K.

To help determine the structures of the observed radical species, we performed ESR spectroscopy of ¹³C labeled enediynes (**1b** and **1c**)¹⁵ (Figure 1B and 1C). There was no significant broadening compared to the spectrum of **1a** (Figure 1A). Considering the reported value of ¹³C hyper-fine-splitting constant of phenyl radical ($a^{13\text{C}-\alpha} = 12.25$ mT),¹⁸ it is unlikely that the spin density is localized at the ¹³C labeled C3 or C6 position; rather, the unpaired radical should exist far from C3 and C6. Our previous spin-trapping



Scheme 2. Proposed pathways from **1** to the relatively stable radicals (**9** and **10**) through *p*-benzyne (**2**) and phenyl radicals (**5** and **6**).

study indicated that the more exposed C6 position of *p*-benzyne biradical (**2**) is more reactive than at the sterically shielded C3 position and the C6 position more readily undergoes hydrogen abstraction.⁹ We propose that **9** and **10** are the radical species stable enough to be detected by ESR, and we propose that the reaction pathways from **2** to produce **9** and **10**, which can be continuously supplied through the equilibrium between **1** and **2** (Scheme 2). The oxygen-stabilized benzyl radical (**9**) would be formed through intermolecular hydrogen abstraction from **7** and/or, less likely, through intramolecular 1,3-transfer¹⁹ (path a) of the benzylic hydrogen in the C3-phenyl radical (**5**), which can be produced at the higher rate than C6-phenyl radical (**6**). The benzylic epoxide hydrogen of **8** would be abstracted, and/or the benzylic hydrogen of **6** might be transferred in a 1,3-fashion¹⁹ to C6-phenyl radical (path b), and subsequent epoxide opening could yield the highly delocalized and more stable radical (**10**), which would accumulate in larger quantity than **9** at the higher temperatures. Thus, it is most likely that the highly

temperature-dependent ESR signal is due to **10** and another signal that predominates at lower temperatures is due to **9**.

In conclusion, bicyclo[7.3.0]epoxydodecadienediyne systems display steady ESR spectra in solution at room temperature because of their spontaneous Masamune-Bergman cyclization to *p*-benzyne biradicals and the equilibrium between the two forms. The current results indicated that the paramagnetic species should not be directly attributed to the *p*-benzyne biradicals but rather to more stable secondary radical intermediates. These results recall the intriguing events that occur in the nine-membered enediyne chromoprotein antitumor antibiotics.^{2,7-9}

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