

THE CONFIGURATION AND CONFORMATION OF
7-CHLORO-1,6-DIBROMO-3,7-DIMETHYL-3,4-EPOXY-1-OCTENE

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7-Chloro-3,7-dimethyl-1,4,6-tribromo-1-octen-3-ol 1 was isolated from the digestive gland of the sea hare, *Aplysia californica*¹. The structure was assigned on the basis of spectral data and by synthesis of a degradation product. NMR studies of the alcohol 1 and the epoxide 2, formed on base treatment, allowed a partial assignment of configuration. The *trans* olefin was identified by a 13.5 Hz vicinal H-H coupling constant, while the *cis* H-CH₃ arrangement about the epoxide ring was established by observing a 15% NOE. To complete the stereochemical description of compounds 1 and 2, we required only the relative configuration at C-6, which could, in principle, be derived from the richly detailed first order 220 MHz nmr spectrum of the epoxide 2. Since the lanthanide induced chemical shift (LIS)^{2,3} not only aided in the interpretation of the nmr spectrum but also revealed the conformation of the epoxide 2, we wish to report our experience with the nmr determination of the topology of the epoxide 2 in solution.



The nmr spectrum of a carefully dried CCl_4 solution of epoxide 2 (from 46 mg of alcohol 1) contained signals which were well enough separated that coupling constants could be accurately estimated from line spacings. Assignment of the resonances to H-1, H-2, H-4 and H-6 was straightforward while the pairs H-5 and H-5', CH₃-8 and CH₃-8' could not be assigned with confidence. Incremental addition of 5 aliquots of Yb(DPM)₃, total=30mg, to the nmr solution dispersed the spectrum in a regular sequence without significantly altering any of the coupling constants. The perturbation in chemical shift at the highest level of Yb(DPM)₃ is listed in Table I as $\Delta\delta^4$.

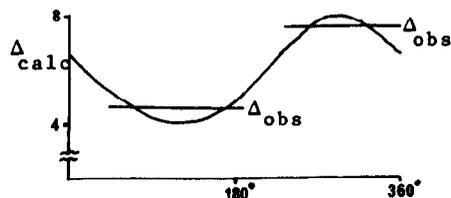
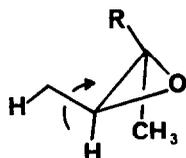
Table I. Observations of LIS behaviors in the presence of Yb(DPM)₃.

Assignment	H-1	H-2	CH ₃ -3	H-4	H-5 or 5'	H-6	CH ₃ -8 or 8'
Δ (ppm)	6.40	6.13	1.79	3.11	2.24 2.55	4.11	1.42 1.65
$\Delta\delta$ (ppm)	3.28	5.30	5.76	10.96	7.06 4.32	3.54	1.05 0.66

Interpretation of LIS values was via our reported procedure, PDIGM⁵. The methods used for testing the conformations of the epoxide were simple modifications of the protocols introduced by Williams⁶, Danyluk⁷, and their collaborators. In this particular case we established in serial order the conformations and/or assignments of 1) H-5 and H-5', 2) H-6 and 3) CH₃-8 and CH₃-8'.

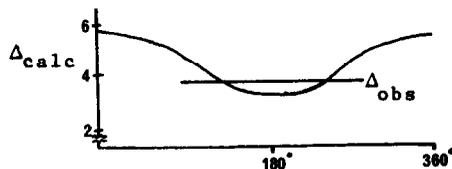
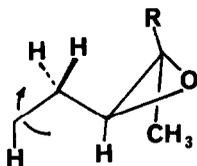
The epoxide 2, having a *cis* arrangement of CH₃-3 and H-4, was modeled for the PDIGM computation and a plot of Yb position vs agreement factor was obtained. Concurrently, several sets of internal coordinates for the hydrogen at C-5 were provided for PDIGM, defining a 0° dihedral angle as that in which H-5 eclipsed H-4 and positive rotation as clockwise about the C-5 to C-4 bond. A hypothetical shift, scaled to the ring resonances, was calculated as a function of H-5 at each location of Yb. The variation in the Yb position for good agreement was large ($2.7 \pm 0.3\text{\AA}$ for Yb-O distance, $\pm 20^\circ$ in and above the plane of the epoxide for R < 5%). The range of $\Delta_{\text{calc}}(\text{H-5})$ values was 2ppm but the shape of the curve was invariant with Yb location. A typical graph is shown in Figure 1, with the maximum and minimum shifts occurring at ca. 240° and 120°. Assignment of signals H-5 and H-5' to these hydrogen positions followed as a matter of course.

Figure 1. Models for and results of calculating hypothetical shifts for H-5 and H-5'.



The second PDIGM computation used the assignments for CH_3 -3, H-4, H-5 and H-5' and the internal coordinates from above to ascertain the Yb locations with $R < 5\%$. A series of dummy atoms for H-6 was also included. A graph of rotamer vs $\Delta_{\text{calc}}(\text{H-6})$ was constructed as before, with the 0° dihedral angle that in which the C6-H6 bond eclipsed the C5-C4 bond (Fig.2). The variation in $\Delta_{\text{calc}}(\text{H-6})$ was small, a direct result of locating the Yb more precisely (Yb-O distance $2.7 \pm 0.2\text{\AA}$, angle variation $\pm 15^\circ$).⁸ Any benefit which might have accrued from this increased precision was removed by the fact that "best fits" occurred for two rotamers. Nothing in the LSR indices and PDIGM method serves to distinguish these possibilities.

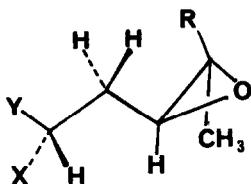
Figure 2. Models for and results of calculating hypothetical shifts for H-6.



Fortunately, we were able to call upon some readily available nmr data, to wit, the couplings $J_{5,6}$ and $J_{5',6}$, which are those expected for *gauche* and *trans* dihedral angles (1.5 and 8 Hz respectively).⁹ The favored conformation for H-6 can be deduced only by taking account of these couplings and the previous assignments of H-5 and H-5'; neither data set (i.e., LIS or coupling constants) is sufficient by itself. The partial structure consistent with all the information at hand is shown in Fig. 3. The configuration at C-6 was determined by assigning the conformational preference of the *gem*-dimethyl group. We used PDIGM for this task by entering the 5 known resonances and computing hypothetical scaled shifts for the 3 staggered rotamers of the dimethyl moiety in each configuration (i.e., the dimethyl group was located at both X and Y in Fig. 3). Inspection of the result of this computation revealed numerous regions in which the experiment was replicated

for the array $X = C(CH_3)_2$, and no such regions for the array $Y = C(CH_3)_2$.

Figure 3.



2. $X = -CCl(CH_3)_2$, $Y = Br$.

We could alter the coordinates of the various hydrogen nuclei by small amounts, up to 0.2\AA , and find many acceptable fits, some of which were "better" than the one we have used. We did not optimize our model because we felt that these alterations were inside the resolution of this particular experiment and that the changes were unlikely to be mathematically significant. The most important feature of this work is that any array in which the conformation and configuration were substantially altered failed to give satisfactory agreement with the LSR shift and coupling constants.

Acknowledgement

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