Simplification of Epoxide and Lactone Proton Magnetic Resonance Spectra Using Tris(dipivalomethanato)europium Shift Reagent[1a]

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The observation by Hinckley[2] that the dipyridine adduct of tris(dipivalomethanato)europium, Eu(DPM)$_3$, caused paramagnetic shifts in the pmr spectrum of cholesterol was closely followed by the discovery that the unsolvated complex was a superior shift reagent.[3] Since then, many articles have appeared describing applications of Eu(DPM)$_3$ to structure determination.[4] While information concerning the extent of paramagnetic shifts for monofunctional compounds is important, data concerning the interactions of shift reagents with polyfunctional compounds are more useful for the structure determination of complex organic compounds. Several groups have reported studies in this area.[5-7] In most of these studies emphasis has been placed on compounds containing sites that complex unequally with Eu(DPM)$_3$. We wish to report our study of the effects of Eu(DPM)$_3$ on the pmr spectra of a series of lactones and epoxides which includes compounds containing two equivalent sites for complexation with Eu(DPM)$_3$. The study of lactones and epoxides is of interest because of their widespread natural occurrence and broad range of physiological activities.

Reference monofunctional compounds studied were 1,2-epoxyoctane (**1**), cyclohexene oxide (**2**), γ-butyrolactone (**3**), and 3aβ,4,5,6,7,7aα-hexahydro-2(3*H*)-benzofuranone (**4**). Difunctional compounds included were the epoxides 1,2,3,4-diepoxybutane (**5**) (isomer mixture) and 1,2,7,8-diepoxyoctane (**6**), and the lactones 4,5-dihydroxyoctanedioic acid bislactone (**7**) and 4,9-dihydroxydodecanedioic acid bislactone (**8**). Compound **1** was prepared from 1-octene by epoxidation with monoperphthalic acid.[8] Compounds **4**, **7**, and **8** were prepared from the corresponding epoxides by the method of Newman and VanderWerf.[9] Chart I summarizes pmr spectral data for representative epoxides and lactones in the presence of Eu(DPM)$_3$. Figure 1 shows the relationship between concentration of epoxide **6** and chemical shift at constant mole ratio of shift reagent to substrate.

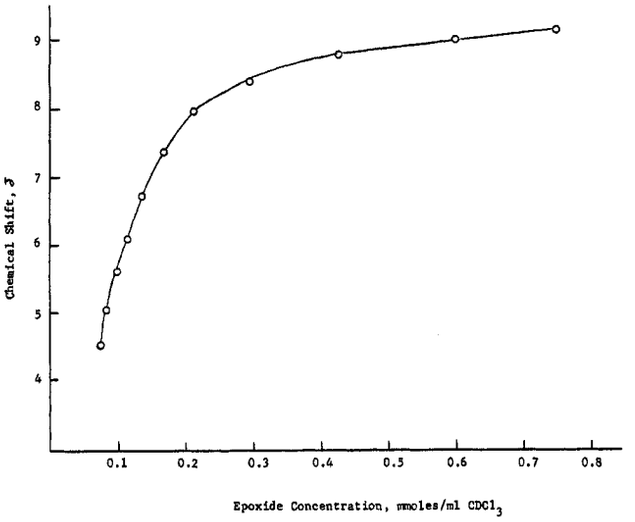
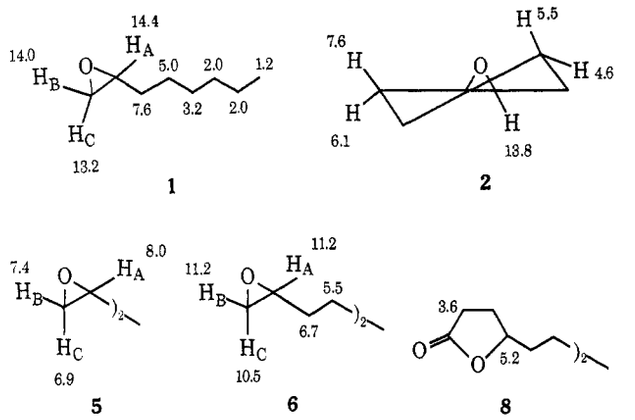


Figure 1.—Chemical shift of methine protons in epoxide **6** as a function of epoxide concentration; Eu(DPM)$_3$:epoxide = 0.5.

CHART I
THE PMR SPECTRA OF EPOXIDES AND LACTONES IN THE PRESENCE OF Eu(DPM)$_3$[a,b]



[a] Epoxide concentration was 1.25 mmol/ml $CDCl_3$; Eu(DPM)$_3$ content, **1**, 0.52 mmol; **2**, 0.19 mmol; **5**, 0.33 mmol; **6**, 0.74 mmol. [b] Lactone concentration was 0.66 mmol/ml $CDCl_3$; Eu(DPM)$_3$ content, 0.13 mmol.

Results and Discussion

Hart and Love[5] have reported the chemical shift of epoxide protons in cyclohexene oxide (**2**) and propylene oxide. Chart I gives more extensive data for **2** which showed sets of signals containing two protons each. The assignments presented were determined by assuming that protons farthest from the epoxide group would be least affected by shift reagent, and by extrapolating to zero Eu(DPM)$_3$ concentration the straight lines produced when the chemical shift of each signal was graphed against Eu(DPM)$_3$ concentration. The data reported[5] for propylene oxide indicated that signals corresponding to H_A and H_B were inseparable. We observed that the corresponding signals[10] in **1** and **5** were resolved while a single peak was still seen for these resonances in compound **6** at the limit of Eu(DPM)$_3$ solubility. The close proximity of the two epoxide groups in **5** could have accounted for the separation of resonances noted. It was expected that similar resolu-

(1) (a) This research was supported in part by Public Health Service Grant No. CA11715 from the National Cancer Institute. (b) David Ross Fellow, 1969–1971. (c) Abstracted in part from the thesis of B. K., 1969.

(2) C. C. Hinckley, *J. Amer. Chem. Soc.*, **91**, 5160 (1969).

(3) J. K. M. Sanders and D. H. Williams, *Chem. Commun.*, 422 (1970).

(4) J. K. M. Sanders and D. H. Williams, *J. Amer. Chem. Soc.*, **93**, 641 (1971), and references cited therein.

(5) H. Hart and G. M. Love, *Tetrahedron Lett.*, 625 (1971).

(6) T. Okutani, A. Morimoto, T. Kaneko, and K. Masuda, *ibid.*, 1115 (1971), and ref 6 in that article.

(7) H. van Brederode and W. G. B. Huysmans, *ibid.*, 1695 (1971).

(8) T. W. Craig, C. R. Harvey, and G. A. Berchtold, *J. Org. Chem.*, **32**, 3743 (1967).

(9) M. S. Newman and C. A. VanderWerf, *J. Amer. Chem. Soc.*, **67**, 233 (1945).

(10) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, New York, N. Y., 1969, p 228.

tion could be obtained for **6** if the epoxide signals could be shifted beyond δ 11.7. While investigating the latter point we observed an apparently hitherto unreported effect of substrate concentration upon resolution of resonances.

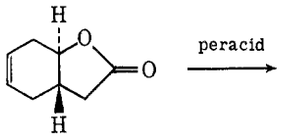
Published data concerning shift reagents has implied that barring effects due to line broadening the resolution of overlapping signals increases as the signals are shifted downfield. However, our data for epoxides **1** and **5** show that resolution of resonances H_A and H_B is achieved at lower chemical shifts when the epoxide concentration is high (1.25 mmol/ml $CDCl_3$) than when the epoxide concentration is low (0.13 mmol/ml $CDCl_3$) although the mole ratio of shift reagent to epoxide was larger (0.92 *vs.* 0.20) in the latter case. This information emphasizes that substrate concentration is as important a factor in the proper use of shift reagents as is the mole ratio of shift reagent to substrate.

Recently, Tomic and coworkers[11] showed that the magnitude of shift experienced by a given set of protons diminished with dilution. Variation over a wide concentration range could not be determined because only one dilution was measured. Compound **6** shows the same overall behavior (Figure 1) upon dilution, with the most pronounced changes occurring at low concentrations. The increased shift caused by dilution could be counterbalanced by adding more shift reagent. The shift observed in the usual experiment is the difference between the downfield shift produced by adding shift reagent and the upfield shift caused by dilution.

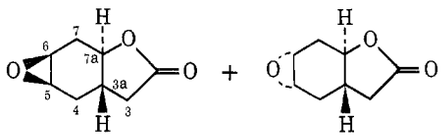
At the concentrations of epoxides and shift reagent used the chemical shift difference ($\Delta\delta = \delta_{Eu} - \delta_{CDCl_3}$) for a given proton varied in proportion to the amount of shift reagent per epoxide group. Thus, at the same concentration of epoxide and shift reagent $\Delta\delta$ for **1** was twice that measured for **6** (3.1 *vs.* 1.6). The same dependence was not seen for the lactones. The effect may be obscured by the much smaller shift experienced by the lactone protons (δ 1–2 at the concentrations studied) due to their weaker association with Eu(DPM)$_3$ compared with epoxides.

Without Eu(DPM)$_3$, only the protons on carbon adjacent to the lactone oxygen were resolved completely; the remaining signals were contained within a broad multiplet. Addition of Eu(DPM)$_3$ caused the signals for protons α to the carbonyl group to experience the greatest shift. These data agree with reports concerning the interaction of Eu(DPM)$_3$ with esters[5] and δ-valerolactones[12] that place the site of complexation at the carbonyl oxygen.

An interesting example of the use of Eu(DPM)$_3$ occurred in the analysis of the reaction products from the epoxidation of **9** with monoperphthalic acid. Column chromatography of the reaction mixture yielded an apparently homogeneous oil on the basis of tlc and spectral data. Elemental analysis established the molecular formula $C_8H_{10}O_3$. However, analysis of the pmr spectrum with Eu(DPM)$_3$ [1.25 mmol of **10**: 0.265 mmol of Eu(DPM)$_3$] showed that the product was a mixture of isomeric epoxylactones **10a** and **10b** in the ratio 6:4. The 7a protons were well resolved (5.4



9



10a **10b**

and 6.6 ppm), and the signal farthest downfield was assigned to the 7a proton which is cis to the epoxide group in compound **10b**. The chemical shift of protons 5 and 6 in **10** is less than that noted for cyclohexene oxide (**2**) measured under comparable conditions. Thus, complexation is occurring at both the lactone and epoxide moieties. The pronounced effect of the epoxide group upon the 7a protons in **10** in the presence of Eu(DPM)$_3$ suggests that this group would be a valuable derivative for studying the structure and stereochemistry of cyclic olefins.

Experimental Section[13]

Preparation of 3aβ,4,7,7aα-Tetrahydro-2(3*H*)-benzofuranone (9).—4,5-Epoxycyclohexene was treated according to the method of Newman and VanderWerf,[9] and gave a 43% yield of crude lactone. An analytical sample was prepared by column chromatography over silicic acid followed by sublimation [45–48° (20 mm)] to give white needles: mp 56.5–58°; nmr δ 5.63 (s, 2, CH=CH), 4.00 (s, 1, CHO), 2.21 (m, 7, CH_2, CH); ir ($CHCl_3$) 5.64 (C=O, γ-lactone), and 6.13 μ (C=C); mass spectrum *m/e* 138 (M^+).

Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.76; H, 7.31.

Preparation of 3aβ,4,5,6,7,7aα-Hexahydro-5,6-epoxy-2(3*H*)-benzofuranone (10).—To 2 g (0.015 mol) of 3aβ,4,7,7aα-tetrahydro-2(3*H*)-benzofuranone (**9**) was added dropwise with stirring 2.64 g (0.015 mol) of monoperphthalic acid in 23 ml of ethyl ether, and the solution was stirred in the dark at room temperature for 24 hr. A precipitate (1.5 g) of phthalic acid was removed by filtration, and the ether filtrate was mixed with solid potassium carbonate until effervescence ceased. The solution was dried (anhydrous sodium sulfate) and concentrated to give 1.35 g of a mixture containing (nmr) **9** and **10** in the ratio of 80:20. Purification was achieved by column chromatography (silicic acid). Elution with benzene removed **9**, and benzene–chloroform (1:1) removed 400 mg of **10** (18% yield). The sample was homogeneous by tlc, but resisted attempts to crystallize it: nmr δ 3.94 (broad s, 1, HCO, lactone), 3.26 (broad d, separation 4.5 Hz, epoxide), 2.21 (m, 7, CH_2, CH); mass spectrum *m/e* 154 (M^+).

Anal. Calcd for $C_8H_{10}O_3$: C, 62.32; H, 6.54. Found: C, 61.84; H, 6.84.

Data Relating to the Separation of Resonances for H_A and H_B in Compounds 1, 5, and 6.—Under conditions described in Chart I partial separation of resonances was achieved when signals were shifted to δ 10.6 in **1**, and 6.5 in **5**. At larger mole ratio (0.92), but lower epoxide concentration (0.13 mmol/ml $CDCl_3$), resolu-

(11) L. Tomic, Z. Majerski, M. Tomic, and D. E. Sunko, *Chem. Commun.*, 719 (1971).

(12) F. I. Carroll and J. T. Blackwell, *Tetrahedron Lett.*, 4173 (1970).

(13) All melting points are uncorrected. The infrared spectra were measured with a Perkin-Elmer 21 spectrophotometer. Mass spectra were obtained using a Hitachi RMU-6A spectrometer. Pmr spectra were determined at 60 MHz with a Varian A-60A or Jeolco Minimar (JNM-MH-60-II) spectrometer. The chemical shift values are expressed in δ values (parts per million) relative to TMS internal standard. Chloroform-*d* was the solvent for pmr spectra. For studies of shift reagent the sample temperature was maintained at 28 ± 1°. The Eu(DPM)$_3$ content of the solution was increased gradually until the desired resolution was obtained. Solution compositions are expressed as the number of mmoles of Eu(DPM)$_3$ and epoxide added to 1 ml of $CDCl_3$. Unless otherwise noted the term "mole ratio" refers to the fraction Eu(DPM)$_3$/substrate. Physical data are recorded only for new compounds. Elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Compounds **2**, **3**, **5**, and **6** were obtained commercially, and were used without further purification.

tion was not obtained until the epoxide signals in **5** were shifted to δ 15.

Registry No.—**1**, 2984-50-1; **2**, 286-20-4; **5**, 1464-53-5; **6**, 2426-07-5; **9**, 34905-87-8; **10a**, 34905-88-9; **10b**, 34905-89-0; Eu(DPM)$_3$, 15522-71-1.

Photolysis of 2,6-Di-*tert*-butyl-4-alkylphenols with Polyhalomethanes

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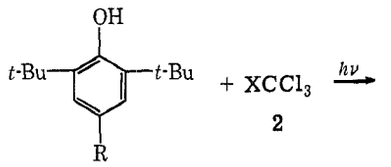
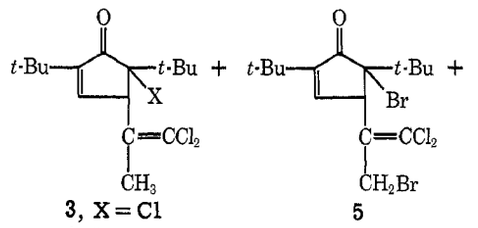
In recent years, a number of studies on photochemical reactions of sterically hindered phenols with various solvents have been published.[1] However, as yet there is little information on the photoreactions of such phenols with polyhalomethanes.

When solutions of 2,6-di-*tert*-butyl-*p*-cresol (**1a**) or 2,4,6-tri-*tert*-butylphenol (**1b**) in either carbon tetrachloride or bromotrichloromethane were irradiated with near-ultraviolet light, two types of photoproducts involving the addition of either a halogen atom or a trichloromethyl radical to the phenol were obtained. The product mixture obtained depended on the structure of the phenol, the solvent used, and, for **1a**, the wavelength of the light used.

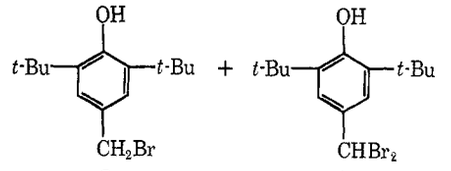
The cyclopentenone **3** was the major product of the photolysis of **1a** in carbon tetrachloride when either 300- or 350-nm light was used. When irradiated with 300-nm light in bromotrichloromethane, **1a** gave about



1a, R = CH_3
b, R = *t*-Bu



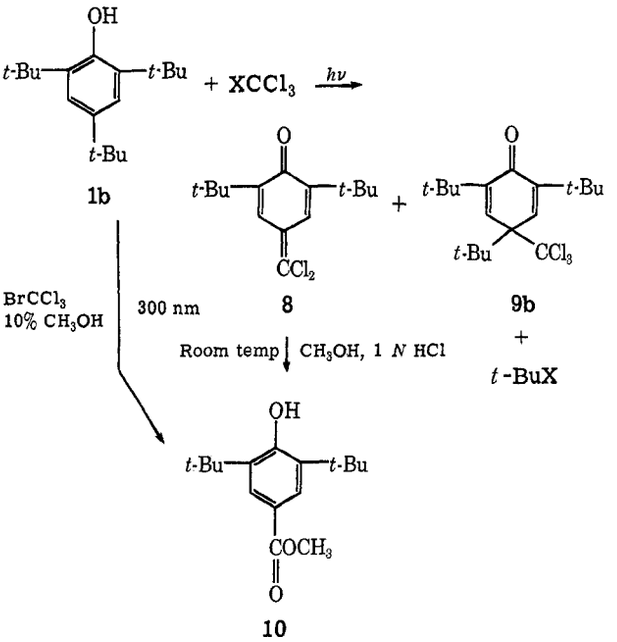
3, X = Cl
4, X = Br
5



6 **7**

65 mol % of the cyclopentenones **4** and **5** along with 20 mol % of the α-brominated phenol **7**, but, when irradiated with 350-nm light, **1a** gave more of the α-brominated phenols **6** and **7** (40% total) than the cyclopentenone **4** (25%).

The photolysis of **1b** in either carbon tetrachloride or bromotrichloromethane gave the cyclohexadienones **8** and **9b** as well as a *tert*-butyl halide. The same products were obtained whether 300- or 350-nm light was used, but the use of 350-nm light resulted in a much lower conversion of **1b**. Moreover, **10** was produced either by irradiating **1b** in bromotrichloromethane containing 10% methanol or by stirring a mixture of **8** in methanol containing 1 *N* HCl at room temperature for 1 hr.



The thermal reaction of **1a** or **1b** with bromotrichloromethane at 160° in the dark gave only a low yield of chloroform and black tar. Neither 2,2′-azobis(2-methylpropionitrile) (AIBN) nor benzoyl peroxide increased the rate of reaction of **1a** or **1b** with bromotrichloromethane at 80° in the dark. These results, taken with the abilities of **1** and **2** to absorb light at 300 and 350 nm,[2] probably indicate that the excitation of phenol[3] and the rate of generation of a halogen atom and a trichloromethyl radical are the vital factors in the photochemical reactions of **1** with a halotrichloromethane. Therefore, a short-chain or nonchain radical mechanism, as shown in Scheme I, probably accounts for the first stage of these photolyses.

Since carbon tetrachloride does not absorb light in the 350-nm region, the photolyses of **1a** and **1b** in carbon tetrachloride were probably initiated by the excitation of phenol followed by an energy transfer to the carbon tetrachloride, which decomposed to give a chlorine atom and a trichloromethyl radical. These fragments subsequently reacted with phenol to form products. The mechanism shown in Scheme I is consistent with the relative rates of disappearance of **1a** and **1b**; **1a**, which

(1) (a) H. D. Becker, *J. Org. Chem.*, **32**, 2115 (1967); (b) T. H. Matsuura, Y. Hiromoto, A. Okada, and K. Ogura, *Tetrahedron Lett.*, 3727 (1970).

(2) The optical densities of **1** (0.335 *M* in CH_2Cl_2) and $XCCl_3$ in a quartz tube (i.d. 1.3 cm) are at 300 nm **1a** = 126, **1b** = 1.3, $BrCCl_3$ = 52, CCl_4 = 0.007; at 350 nm, **1a** = 3.0, **1b** = 1.1, $BrCCl_3$ = 0.7, CCl_4 = 0. The spectral distribution of an RPR 350-nm lamp ranges from 307 to 420 nm with the maximum emission at 350 nm.

(3) K. Omura and T. Matsuura, *Tetrahedron*, **26**, 255 (1970).