Solvent-Dependent Hydroxyl Proton-Proton Coupling in *syn*-Hydroxy Epoxides

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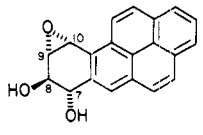
Received January 4, 1980

In the course of enzymatic detoxification, significant proportions of the carcinogenic polycyclic hydrocarbons, such as benzo[*a*]pyrene, are converted via epoxidation and subsequent hydration to *trans*-dihydrodiols.[1] Further oxidation of the dihydrodiols to diol epoxides (e.g., **1** and **2**) may lead to deleterious in vivo effects resulting from diol epoxide binding to proteins, DNA and RNA.[2-4]



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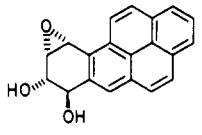

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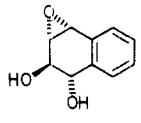

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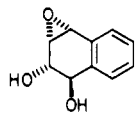

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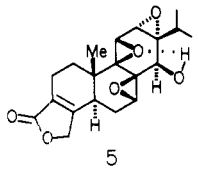
In an early paper,[5] Hulbert predicted that hydrogen bonding in the *syn*-diol epoxides (e.g., **1** and **3**) between the epoxide oxygen and a pseudoaxial β-OH group (e.g., at C7 in **1**) would enhance the reactivity of the syn isomers toward nucleophiles. Similar effects have been proposed to account for the reactivity of the antileukemic plant principles triptolide (**5**) and tripdiolide,[6] the 8,9-epoxide



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of picrotoxinin,[7] and certain epoxy sterols.[8,9] In the *anti*-diol epoxide isomers such as **2** or **4** neither OH group is well-situated to hydrogen bond to the epoxide,[10] and the entropic advantage of an internal hydrogen bond cannot be manifested. Hulbert's prediction has been borne out, in part, by nucleophilic-addition studies which have shown dramatic rate accelerations to *syn*-diol epoxides **1** and **3** relative to their anti isomers (**2** and **4**), though only in certain solvent systems.[11] Herein we present results of a ^{1}H NMR study of *syn*-2-hydroxyindan 3a,7a-oxide (**6**)[12] and discuss their relevance to the solvent dependence for nucleophilic additions to **1** and **3**.

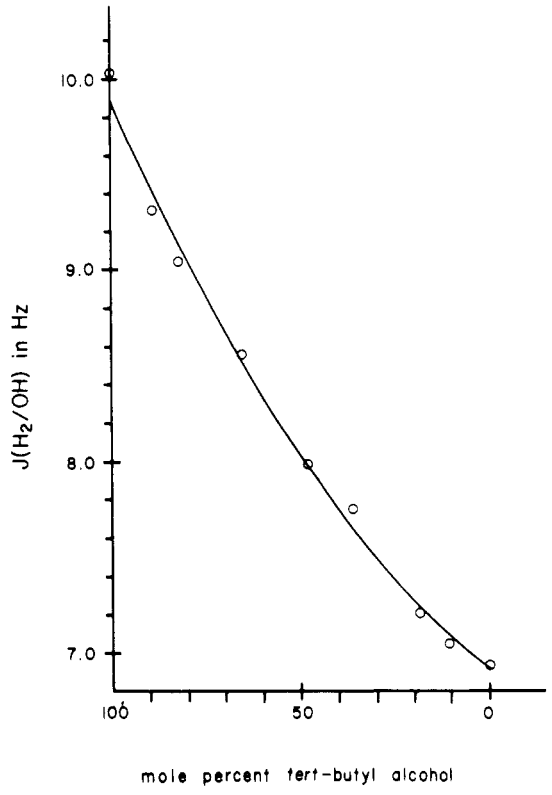

Figure 1. Observed coupling $J(H_2/OH)$ for *syn*-2-hydroxyindan 3a,7a-oxide as a function of solvent composition in *tert*-butyl alcohol/dimethyl-d_6 sulfoxide mixtures. The nine points are measured values; the line is a plot of eq 1.

Results and Discussion

The ^{1}H NMR spectrum of *syn*-2-hydroxyindan 3a,7a-oxide (**6**) shows a large solvent dependence. In the weakly hydrogen-bonding solvent $CDCl_3$, the hydroxyl proton is intramolecularly associated with the epoxide (conformation **6a**).[12] The large coupling of H_2 and the OH ($J(H_2/OH)$ = 11.4 Hz) in $CDCl_3$ is diagnostic of the antiperiplanar relationship of the coupled protons. A similar coupling is measured in $CDCl_3$ between the corresponding protons in triptolide (**5**, J = 11 Hz).[6a] In *tert*-butyl alcohol (*un*-deuterated) the exchange of the hydroxyl proton of **6** with the solvent hydroxyl protons is slow, relative to the NMR time scale, and the coupling $J(H_2/OH)$ can be measured ($J(H_2/OH)$ = 10.0 Hz). The value still indicates a predominance of conformation **6a**. Figure 1 shows the dependence of $J(H_2/OH)$ as the solvent composition is varied from 100 mol % *tert*-butyl alcohol to 100 mol % dimethyl-d_6 sulfoxide. In the strongly hydrogen-bonding solvent, dimethyl-d_6 sulfoxide, the hydroxyl proton becomes associated with solvent, disrupting the hydrogen-bonded conformation **6a** and lowering the measured coupling ($J(H_2/OH)$ = 6.9 Hz). In dimethyl-d_6 sulfoxide, the

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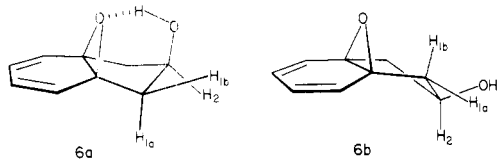
0022-3263/80/1945-3534$01.00/0

observed couplings $J(H_{1b}/H_2)$ and $J(H_{1a}/H_2)$ indicate that **6** may be conformationally mobile, showing contributions from both extremes of geometry, **6a** and **6b**.[12]



The coupling $J(H_2/OH)$ as a function of solvent composition (Figure 1) is closely approximated by the quadratic eq 1, where M represents the mole percent of *tert*-butyl alcohol in the *tert*-butyl alcohol/dimethyl-d_6 sulfoxide mixture. Equation 1 has been derived empirically for the *syn*-hydroxy epoxide **6** and is not intended to apply directly to other systems such as **1** or **3**. Undoubtedly, the coefficients in eq 1 reflect not only the propensity for hydrogen bonding to the epoxide in conformation **6a** vs. hydrogen bonding to the solvent but also reflect the energetics of the conformational change **6a** $\rightleftarrows$ **6b** as hydrogen bonding to solvent molecules becomes significant. Thus, for different conformationally mobile systems the coefficients, if not the nature, of the corresponding equation will change.

$$J(H_2/OH) = [1.53 \times 10^{-4}M^2 + 1.46 \times 10^{-2}M + 6.91]\ \text{Hz} \quad (1)$$

Both conformational[10] and rate data have been obtained for diol epoxides **1**–**4**[11] and other diol epoxides.[13] The data presented herein show that the propensity for *intramolecular* hydrogen bonding in *syn*-diol epoxides such as **1** and **3** may depend critically on solvent composition. Conformational assignments based on ^{1}H NMR spectra obtained in solvents such as dimethyl-d_6 sulfoxide[10,11a,c] need not apply to solvent systems[11,13] used for nucleophilic addition rate studies.

The *syn*-diol epoxides **1** and **3**[11a] and three *syn*-diol epoxides derived from benzo[*a*]anthracene[13] react with *p*-nitrophenylthiolate from 60 to 330 times faster than their corresponding anti isomers in 98 mol % *tert*-butyl alcohol/2 mol % dimethyl sulfoxide. By contrast, in 25% EtOH/75% aqueous buffer (pH 7.4), diol epoxides **3** and **4** react at nearly equal rates, the anti isomer actually reacting somewhat faster.[11a] The pronounced solvent dependence has been ascribed to conformational effects in the alcohol/water system.[11a] The present results clearly show that *intramolecular* hydrogen bonding will be enhanced in *syn*-diol epoxides (cf. Figure 1) in 98% *tert*-butyl alcohol/2% dimethyl sulfoxide. In the alcohol/water system hydrogen bonding to the solvent may be dominant. The entropic advantage of an *intramolecular* hydrogen bond, thus, will be manifested only in the nonaqueous solvent system. A similar rate effect is seen for isomers **3** and **4** in dioxane/water mixtures. The rate acceleration for the syn isomer **3**, seen as the proportion of the organic solvent increases, has been discussed also by Bruice.[11c]

Rate studies for nucleophilic addition of thiolates to **6** in *tert*-butyl alcohol/dimethyl sulfoxide mixtures were precluded by the lack of reactivity of *p*-nitrophenylthiolate toward **6**. Other thiolates, such as LiSMe which is known to add to **6** in *tert*-butyl alcohol/water,[12] cannot be used due to their low solubility in *tert*-butyl alcohol/dimethyl sulfoxide mixtures. The instability of **6** in *tert*-butyl alcohol/water[12] precludes as well kinetic measurements in this solvent system.

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Experimental Section

^{1}H NMR of *syn*-2-Hydroxyindan 3a,7a-Oxide (6). The epoxy alcohol (**6**) was prepared by our published procedure.[12] Solutions of **6** (0.2 M) were prepared in volumetrically measured mixtures of *tert*-butyl alcohol (J. T. Baker, reagent grade dried statically over activated 4-Å molecular sieves) and dimethyl-d_6 sulfoxide (Merck, 99.5%). Nine samples prepared in this fashion contained 100, 89.0, 82.2, 65.3, 48.1, 36.2, 18.5, 10.9, and 0 mol % *tert*-butyl alcohol. The last sample, containing only dimethyl-d_6 sulfoxide as solvent, also contained ca. 1% tetramethylsilane (for spectrometer lock). The hydroxyl region of the ^{1}H NMR spectrum of **6**[12] was swept at a rate of 1.0 Hz/6.0 s with a sweep width of 50.0 Hz (Hitachi Perkin-Elmer R-24B NMR spectrometer). The spectrometer was locked on the *tert*-butyl alcohol methyl signal for all samples except the dimethyl-d_6 sulfoxide sample which was locked on internal tetramethylsilane. The hydroxyl region in each sample was swept four or five times and the average observed couplings were calculated: 10.03 Hz (100 mol % *tert*-butyl alcohol), 9.31 Hz (89.0 mol%), 9.04 Hz (82.2 mol%), 8.56 Hz (65.3 mol%), 7.98 Hz (48.1 mol%), 7.75 Hz (36.2 mol%), 7.20 Hz (18.5 mol%), 7.04 Hz (10.9 mol%), 6.93 Hz (0 mol%). The pooled standard error of $J(H_2/OH)$ from all measurements is 0.04 Hz (38 measurements and 9 average observed couplings or 29 degrees of freedom). This represents the standard error for our method of measurement of $J(H_2/OH)$, irrespective of solvent composition.

Curve Fitting. The coupling constant data were curve fitted by quadratic regression on Texas Instruments calculator SR52, using program number ST1-13. The standard error of the fit of the nine average observed couplings to eq 1 is 0.10 Hz (6 degrees of freedom).

Acknowledgment is made to the National Institutes of Health (grant number CA 20574) for support of this work. We thank Mr. Paul Bergstein for valuable assistance.

Registry No. 6, 19439-32-8.

Synthesis of Seleno and Telluro Isocoumarins: 1*H*-2-Seleno- (and -Telluro-) benzopyran-1-ones

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Received March 27, 1980

Although seleno[1] (and telluro)[2] chromones (4*H*-1-seleno- (and -telluro-) benzopyran-4-ones) as well as seleno[3] (and -telluro)[4] coumarins (2*H*-1-seleno- (and -telluro-) benzopyran-2-ones) have been synthesized, their isomers, isoseleno- (and isotelluro-) coumarins **3** are still unknown. In order to investigate the chemical and physicochemical properties of compounds of the three isomeric series, we needed a synthesis of chalcogenated isocoumarins. This was accomplished in a three-step reaction pathway (Scheme I). Ethyl *o*-ethynylbenzoate **1** is readily available from ethyl *o*-acetylbenzoate by classical reaction with phosphorus pentachloride–pyridine[5] or from ethyl *o*-iodobenzoate by bis(triphenylphosphine)–palladium dichloride catalyzed cross-coupling reaction with acetylene.[6] The triple bond of this ester undergoes easily the regiospecific nucleophilic β-addition of the methaneselenolate (or -tellurolate) anion, affording the chalcogenated esters

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