Intramolecular Hydrogen Bonding. An Infrared and Nuclear Magnetic Resonance Study of Diastereomeric Episulfides[1]

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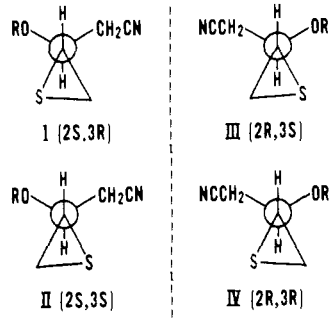
Abstract: A detailed ir and nmr study has confirmed the absolute configurational assignments of diastereomeric β-hydroxy (-acetoxy) episulfides. The concentration dependence of the bonded and free hydroxyl absorptions of the alcohols shows that the isomer previously assigned the *2S,3R*, or threo configuration (I, R = H) forms the stronger intramolecular hydrogen bond ($\Delta\nu$ = 138 cm^{-1}), whereas the isomer assigned the *2S,3S*, or erythro configuration (II, R = H, $\Delta\nu$ = 123 cm^{-1}) has a greater tendency to associate intermolecularly (dimers) in carbon tetrachloride. Chloroform may be a better solvent than generally thought for differentiating between closely related isomers that have relatively weak internal hydrogen bonds. Our results indicate that chloroform is a good solvent for estimating the relative strengths of intramolecular hydrogen bonds of the diastereomeric β-hydroxy episulfides, since chloroform efficiently disrupts interfering weaker intermolecular bonds at episulfide concentrations below 0.03 *M* while it has little effect on the intramolecular hydrogen bonds. The OH proton chemical shift for either isomer is linearly dependent upon concentration, the threo alcohol exhibiting a smaller limiting slope but larger limiting chemical shift compared with the erythro alcohol. The strong HCOH coupling (J_{HCOH} = 9.0 ± 0.3 Hz) found for the threo alcohol at all concentrations studied contrasts with the smaller coupling ($J_{HCOH} \cong$ 2–3 Hz) for the erythro isomer observed only at low concentrations (<0.007 *M*). The methylene protons of the episulfide ring (H-4 and H-5) are part of an ABX system with H-3 in both isomers, but in the erythro alcohol this pattern collapses to an AA'X system in dilute chloroform solution (below 0.084 *M*) apparently as a result of specific interaction with chloroform. Benzene-induced solvent shifts for protons of the acetates suggest an interaction in which the planes of the benzene and episulfide rings are approximately perpendicular.

We previously reported[3,4] the isolation and characterization of diastereomeric pairs of β-hydroxy episulfides, 1-cyano-2-hydroxy-3,4-epithiobutanes, which are formed on enzymic hydrolysis of thioglucosides [potassium (*S*)- and (*R*)-2-hydroxy-3-butenylglucosinolates] in the seeds of *Crambe abyssinica* (isomers I and II) and *Brassica napus* (isomers III and IV, R = H). Whereas the absolute configurations at C-2 of the pairs of diastereomers [2(*S*) for I and II, 2(*R*) for III and IV] were established unequivocally by chemical means,[3-7] the absolute configurations at C-3 (Chart I) have been assigned tentatively[4] on the basis of the empirical generalization proposed by Kuriyama and coworkers[8] concerning the sign of the Cotton effect in the optical rotatory dispersion (ORD) curves of steroidal episulfides.

Chart I



To our knowledge the validity and generality of the episulfide sector rule[5] have not been established for acyclic molecules. Therefore we sought additional evidence for the absolute stereochemistry of the episulfides I and II on the basis of the following considerations.

A priori, rotamers shown above (Chart I) are expected to be major contributors to the conformational equilibria of the acetates (R = Ac), whereas in the hydroxy compounds (R = H) the rotational distribution could be altered significantly as a result of intramolecular hydrogen bonding. In theory each of the diastereomers can form intramolecular hydrogen bonds (OH···S), and the strengths of these bonds and the populations of the bonded rotamers should be a function of the respective steric environments about the C-2–C-3 bond. On this basis the alcohol previously assigned[4] the threo configuration (I-OH) should show more intramolecular O–H···S association than the isomer assigned the erythro configuration (II-OH),[9] whereas the favored rotamer of the latter alcohol is better suited for linear (intermolecular) association. No previous report of intramolecular hydrogen bonding in β-hydroxy episulfides is known to us, although similar internal association has been reported between hydroxyl and thioether linkages[10-14] and in epoxy alcohols.[15-20]

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We determined the relative extent of hydrogen bonding in the diastereomers I and II (R = H) by (1) measuring the concentration dependence of the hydroxyl absorption from ir spectra of the two alcohols and (2) observing the dilution shift of the hydroxyl proton in the nmr spectra of each isomer. In addition, since the magnitude of the vicinal proton coupling constant ($J_{2,3}$) is a measure of the relative populations of the various conformations,[21-26] we examined in detail the proton chemical shifts and coupling constants of the diastereomers I and II (R = H, Ac). The threo and erythro assignments derived from these data, in conjunction with the known absolute configurations at C-2, enabled us to assign absolute configurations at C-3 and to verify the previous assignments obtained from ORD data.

Results and Discussion

Infrared Study. Hydroxyl bands in the 3600-cm^{-1} region in the ir spectra of I and II (R = H) were examined in carbon tetrachloride (0.0017–0.0370 *M*) and chloroform (0.008–0.086 *M*). Ir data were obtained in the weakly associative solvent, chloroform, so that ir interpretations could be extended to the companion nmr study, where the limited solubility of the alcohols in carbon tetrachloride necessitated the use of chloroform. At concentrations lower than 0.007 *M* each episulfide shows two concentration-independent OH bands, which are assigned to free (3589–3618 cm^{-1}) and intramolecularly bonded (3456–3495 cm^{-1}) hydroxyl groups. Internal hydrogen bonding observed for I-OH and II-OH is due to OH···S bonding and not to OH···nitrile interaction as shown both by the size of $\Delta\nu$ and by the fact that (*S*)-1-cyano-2-hydroxy-3-butene[4,7] exhibits only free OH absorption (3625 cm^{-1}) at concentrations less than 0.005 *M*. Pertinent ir data are shown in Table I.

In interpreting the ir data we assume that an equilibrium (eq 1) exists among rotamers with free (ROH)

$$n\mathrm{ROH} \rightleftharpoons (\mathrm{ROH})_n \qquad (1)$$

and bonded [$(ROH)_n$] hydroxyl groups and that at concentrations less than 0.005 *M* these species are monomers (n = 1).[9] Hydroxyl stretching bands observed for intermolecular hydrogen bonds have greater band widths and molar absorptivities than free OH bands.[27] It is often assumed that free and intramolecularly bonded OH bands have equal absorptivities, an assumption more likely to be valid[13,28] if the two types of bands are of equal width. A more rigorous parameter is the integrated band intensity, which depends upon a knowledge of the band widths.[13] Since the free and bonded OH band widths (*ca.* 36 and 74 cm^{-1}, respectively) were not the same for the episulfides, we estimated the band intensities from the apparent band areas,[28] A^a (eq 2), for each band from the apparent peak absorbances, A = log $(I_0/I)\nu_{max}$, and the apparent half-intensity band widths, $\Delta\nu_{1/2}{}^a$. These band areas (intensities) are plotted as a function of episulfide concentration in Figures 1 and 2. Apparent "equilibrium" constants, K_a, for eq 1 may be estimated from these plots at low concentrations where n = 1 (eq 3 and Table I, $K_a = K$ when $\epsilon_b = \epsilon_f$). Here $(ROH)_n$ represents intramolecularly bonded species. At

$$A^a = 2.303A(\pi/2)(\nu\Delta_{1/2}{}^a) \qquad (2)$$

higher concentrations, where $n > 1$, K_a increases as a function of episulfide concentration (Figure 3).

$$K_a = \frac{A_{\text{bonded}}{}^a}{A_{\text{free}}{}^a} \propto \frac{[(\mathrm{ROH})_n]}{[\mathrm{ROH}]} \qquad (3)$$

Table I shows that in each solvent the threo alcohol (I-OH) exhibits (1) a larger frequency shift, $\Delta\nu$, and (2) a larger K_a value than the erythro isomer (II-OH), observations that are consistent with proportionately more and stronger intramolecular hydrogen bonding in the threo alcohol.[27,28a,29,30a] Both isomers exhibit a larger $\Delta\nu$ than reported for a number of hydroxy thioethers.[10-14]

From eq 4–6 we see that the bonded OH intensity is proportional to the episulfide concentration raised to a power, n. Figure 1 clearly shows the differences between the two isomers in their abilities to intra-

$$[(\mathrm{ROH})_n] = K[\mathrm{ROH}]^n \qquad (4)$$

$$A_{\text{bonded}}{}^a \propto [(\mathrm{ROH})_n] \qquad (5)$$

$$A_{\text{bonded}}{}^a \propto [\mathrm{ROH}]^n \qquad (6)$$

Table I. Infrared Data for Hydroxy Epithiobutanes

Isomer, solvent	ν_{OH} (free), cm^{-1}	ν_{OH} (bonded), cm^{-1}	$\Delta\nu$, cm^{-1}	K_a[a]
threo, I-OH				
CCl_4	3600	3462	138	2.32
$CHCl_3$	3595	3462	133	2.26
erythro, II-OH				
CCl_4	3618[b]	3495	123	2.01
$CHCl_3$	3612	3495	117	1.44
(*S*)-1-Cyano-2-hydroxy-3-butene	3625[c]	...	...	...

[a] From Figures 1 and 2 and eq 3 (±0.05); <0.007 *M* (CCl_4); <0.04 *M* ($CHCl_3$). [b] Very weak shoulder at 3592 cm^{-1}. [c] In $CHCl_3$; intermolecularly bonded OH band at 3486 cm^{-1} (>0.005 *M*).

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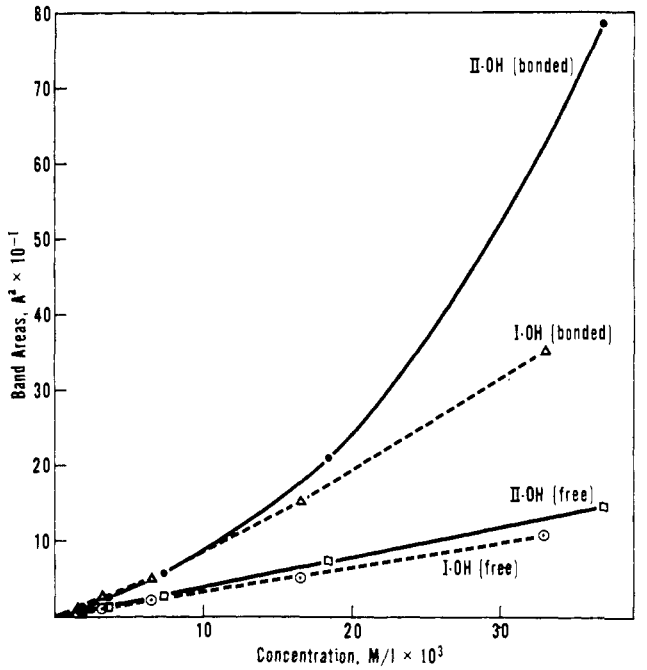


Figure 1. Apparent band areas of hydroxy epithiobutanes as a function of concentration in carbon tetrachloride.

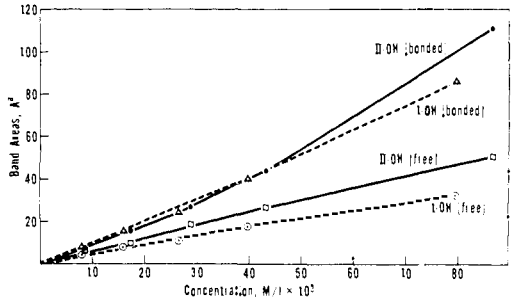


Figure 2. Apparent band areas of hydroxy epithiobutanes as a function of concentration in chloroform.

and intermolecularly hydrogen bond. The importance of intramolecular association ($n = 1$, eq 6) is indicated, since both alcohols give linear plots of $A_{\text{bonded}}{}^{a}$ at concentrations below 0.007 M. However, the sharp increase in intensity of the bonded OH band ($A_{\text{bonded}}{}^{a}$), as well as the corresponding increase of K_a (Figure 3), observed for the erythro alcohol (II-OH) is evidence of its propensity to associate intermolecularly in carbon tetrachloride at concentrations greater than 0.008 M. In fact, in this solvent (0.008–0.037 M) the bonded OH intensity of the erythro alcohol is proportional to the second power of the concentration (*i.e.*, $A_{\text{bonded}}{}^{a}$ *vs.* C^2 is linear), and therefore intermolecular association in this concentration range probably involves dimers.[30b] The threo alcohol (I-OH), with its greater preference for intramolecular hydrogen bonding, shows significantly less deviation of $A_{\text{bonded}}{}^{a}$ from a linear plot even at the highest concentration used (Figure 1). For this alcohol the concentration dependency (C^n) of $A_{\text{bonded}}{}^{a}$ is intermediate between C and $C^{3/2}$ in the range 0.007–0.033 M and indicates a more gradual transition from monomeric to dimeric (or polymeric) association (see also Figure 3).

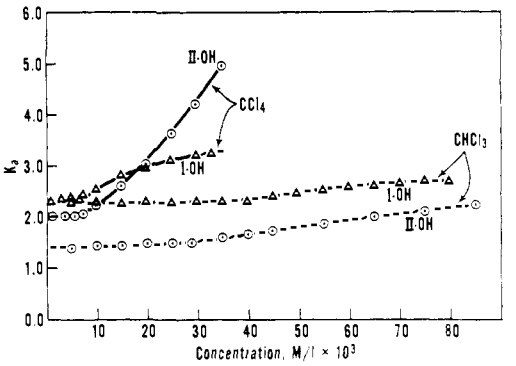


Figure 3. Ratio of bonded to free OH band areas, K_a, as a function of hydroxy epithiobutane concentration.

Chloroform displaces the free OH band of each alcohol to lower frequency compared with carbon tetrachloride but has no influence on the frequency of the bonded OH (Table I). Furthermore, chloroform has little effect on the relative intensities of the free and associated OH bands of the threo alcohol (I-OH) as indicated by the near identity of the K_a values for the two solvents (<0.007 M). These observations suggest that chloroform weakly associates with free hydroxyl groups (hence the frequency shift) but does not appreciably disrupt the intramolecular bonds. Others have reported chloroform shifts for both free and intramolecularly bonded hydroxyl frequencies.[12,13] The erythro isomer (II-OH), however, shows considerably more free hydroxyl absorption in chloroform than in carbon tetrachloride (*cf.* K_a in the two solvents, Table I). Intermolecular association of the erythro alcohol contributes to the bonded OH absorption at 3489 cm^{-1}, since this band is significantly broader than the corresponding band of the threo isomer particularly at concentrations greater than 0.010 M. Apparently chloroform disrupts these intermolecular hydrogen bonds. The marked leveling effect of chloroform on intermolecular association is readily apparent from a comparison of Figures 1 and 2 and from the plot of K_a as a function of episulfide concentration (Figure 3). In Figure 3 the chloroform data are nearly linear, and the slight upward slope of the lines shows that chloroform efficiently reduces intermolecular association. A zero slope (as at low concentration) means that only intramolecular hydrogen bonding is involved, while the larger K_a values for the threo alcohol (I-OH) clearly demonstrate stronger internal hydrogen bonding for this isomer. In fact, our results indicate that chloroform, by removing residual dimeric association, is superior to carbon tetrachloride as a solvent for determining the extent of internal hydrogen bonding in the two episulfides. Certainly comparison of the data obtained in the two solvents gives useful information not derivable from either solvent alone.

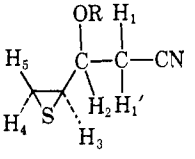
Nmr Studies. Nmr spectra (100 MHz) of the alcohols and acetates (I and II) were obtained in chloroform-*d*, and spectra of the acetates were also examined in carbon tetrachloride and benzene-d_6. The chemical shifts (±0.01 ppm) and coupling constants (±0.2 Hz) are given in Table II. Proton assignments are based on expected chemical shifts and on the interrelation of the observed coupling constants as determined by frequency-sweep double-resonance tech-

Table II. Chemical Shifts (τ) and Coupling Constants (J) for Epithiobutanes (I and II)[a]

Isomer, solvent[b]	τ[c] H-2	H-3	H-1, H-1′	H-4	H-5	Ac-CH_3	J 2,3	1,2 1′,2	3,4	3,5	4,5	1,1′
					threo, I							
I-OH, $CDCl_3$	6.01	6.75	7.32[d]	7.50	7.59		4.0	6.2[e]	6.5	5.1	−1.4	
I-OAc, $CDCl_3$	5.19	6.79	7.16, 7.23	7.41	7.64	7.87	7.1	6.1, 5.5	6.3	5.2	−1.8	−16.9
CCl_4	5.32	6.85	7.22, 7.28	7.44	7.66	7.88	7.4	6.0, 5.4	6.3	5.3	−1.8	−16.7
C_6D_6	5.57	7.30	7.96, 8.09	8.11	8.28	8.40	7.5	5.6, 5.6	6.4	5.2	−1.7	−16.9
C_6D_6 $\Delta^{C_6D_6}_{CCl_4}$	0.25	0.45	0.74, 0.81	0.67	0.62	0.52						
					erythro, II							
II-OH, $CDCl_3$	6.16	6.86	7.26[d]	7.49	7.54		5.3	5.5[e]	6.0	5.1	−1.5	...[f]
II-OAc, $CDCl_3$	5.43	6.89	7.15[d]	7.43	7.52	7.86	8.0	5.1[e]	6.0	5.1	−1.5	...
CCl_4	5.53	6.97	7.29[d]	7.53	7.59	7.92	8.0	5.0[e]	6.0	5.1	−1.5	...
C_6D_6	5.68	7.35	7.96[d]	7.94	8.04	8.37	7.8	5.2[e]	5.8	5.3	−1.5	...
$\Delta^{C_6D_6}_{CCl_4}$	0.15	0.38	0.67	0.41	0.45	0.45						

[a] 100 MHz, probe temperature. [b] Concentrations = 0.50–0.93 *M*. [c] Tetramethylsilane internal standard. [d] Center of (major) doublet. [e] $1/2(J_{1,2} + J_{1',2})$. [f] Chemical shifts are the same; J not observed.

niques (spin decoupling), and are in accord with results reported for epoxides,[31-34] aziridines,[35] cyclopropanes,[36,37] and other episulfides.[34,35,38,39] The assignment of H-5 rather than H-4 to the high-field signal rests on the fact that $J_{cis} > J_{trans}$ for vicinal protons on a three-membered ring[34,35,38] and on the assumption that the magnetic anisotropy of the C-2–C-3 bond makes a greater local-field contribution to the shielding of H-5 than to the shielding of H-4.[35,38] Consequently, in both isomers H-5 is assigned to the proton cis to the alkyl group and H-4 is then cis to H-3. The negative sign of $J_{4,5}$ is assumed from the work of Smith and Cox[34] and of Manatt and coworkers.[35]



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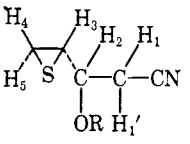


II

In Figure 4 the hydroxyl proton chemical shift (from $CHCl_3$) is plotted as a function of concentration of the two alcohols in chloroform. The linear relationship exhibited by both isomers is indicative of intramolecular association in the concentration range studied,[16] and the smaller limiting slope of the threo (I-OH = 739 Hz/N) compared with the erythro alcohol (II-OH = 1455 Hz/N) is consistent with stronger bonding in the threo alcohol.[16,18,40] The threo alcohol has the larger limiting chemical shift for the hydroxyl proton (I-OH = τ 7.75, II-OH = τ 7.63).

The magnitudes of the vicinal coupling constants, $J_{2,3}$ (Table II), show that rotamers with H-2 gauche to H-3 predominate for the alcohols, whereas rotamers with H-2 antiperiplanar to H-3 predominate for the acetates. Newman projections of rotamers of the threo

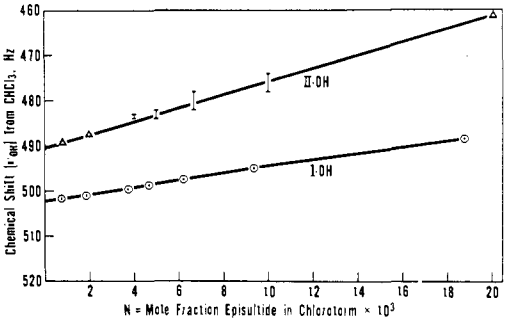
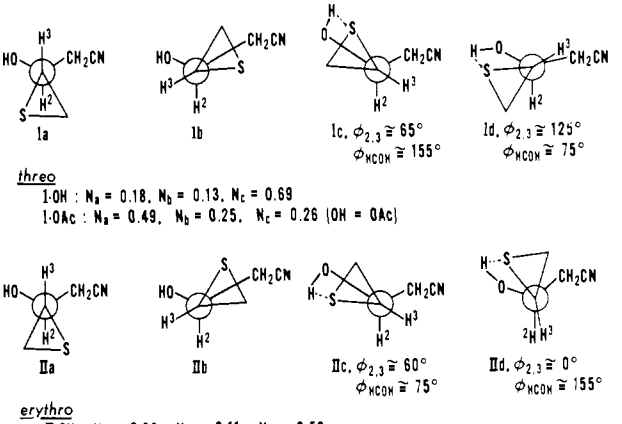


Figure 4. Hydroxyl-proton chemical-shift dependence on concentration of hydroxy epithiobutanes in chloroform-*d*.

(Ia–d) and erythro (IIa–d) isomers are shown in Chart II (OH = OAc for the acetates). The limiting vicinal

Chart II



proton dihedral angles ($\phi_{2,3}$) indicated for the hydrogen-bonded rotamers of the alcohols (Ic,d, $65° \leqslant \phi \leqslant 125°$; IIc,d, $0° \leqslant \phi \leqslant 60°$) are measurements taken from molecular models and within these limits the OH···S distance is 2–2.5 Å. These rotamers (Ic,d, IIc,d) allow for adjustment of the OH···S distance and spatial relationship to attain the maximum hy-

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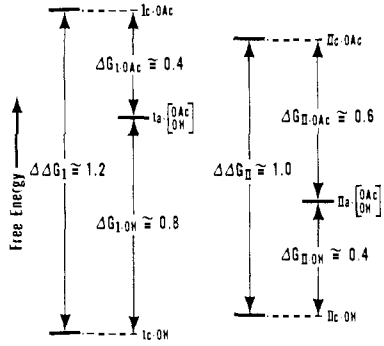

Figure 5. Free-energy relationships for estimating strengths of internal hydrogen bonds of hydroxy epithiobutanes.

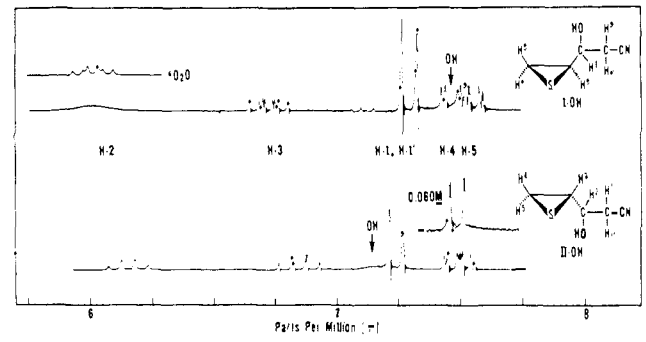

Figure 6. 100-MHz nmr spectra of hydroxy epithiobutanes in chloroform-*d* (0.5 *M*).

drogen bond strength permitted by the geometry of the systems.

Eclipsed rotamers such as Id and IId (Chart II) should contribute little to the conformational distributions and for the most part may be ignored. Furthermore, rotamer Ib (IIb), with the episulfide ring eclipsed with the bulky cyanomethyl group, should be less important than Ia (IIa) or Ic (IIc).[41] Therefore, the observed vicinal coupling constants, $J_{2,3}$ (Table II), are derived primarily from contributions of rotamers with $\phi_{2,3} \cong 180°$ (Ia, IIa) and $\phi_{2,3} \cong 60°$ (Ib,c and IIb,c). An estimate of N_a = mole fraction Ia (IIa) may be obtained from eq 7, where J_a = 11–14

$$J_{2,3} = N_a J_a + (1 - N_a) J_g \qquad (7)$$

Hz = $J_{2,3}$ for Ia (IIa), $1 - N_a = N_b + N_c$ = sum of mole fractions Ib,c (IIb,c), and J_g = 2.2 Hz = $J_{2,3}$ for rotamers with $\phi_{2,3} = 60°$. Further, it is assumed that the values of K_a obtained for the alcohols from their ir spectra at low concentrations in chloroform (I-OH = 2.26, II-OH = 1.44) may be used to approximate the mole fractions of hydrogen-bonded rotamers Ic (N_c = 0.69) and IIc (N_c = 0.59). The mole fractions N_b of Ib and IIb then may be estimated from the combined ir and nmr data (N_d = 0). Values for N_a, N_b, and N_c are given in Chart II. For the acetates (OH = Ac) N_c cannot be evaluated independently of the nmr data, but a reasonable lower limit of N_c is obtained from eq 7 by assuming that $N_b = N_c = {}^1/_2(1 - N_a)$ (undoubtedly $N_c > N_b$,[9,41] for reasons outlined above).

In Figure 5, the free-energy differences, ΔG, are obtained from the ratio of appropriate rotamer populations N_a and N_c. Assuming that the energy of rotamer Ia (IIa) is not changed appreciably by substitution of OAc for OH, the strength of the internal hydrogen bond is given by the difference $\Delta\Delta G$ between Ic-OAc (IIc-OAc) and Ic-OH (IIc-OH). The calculated hydrogen bond strengths are reasonable (I-OH = 1.2 kcal/mol; II-OH = 1.0 kcal/mol) and, in fact, are in good agreement with previous reports for thioether–OH bonds,[13,14] but they must be viewed only as rough approximations. Although qualitatively consistent with the overall findings of this study, the estimated difference in $\Delta\Delta G$ between the two isomers is too small to be judged significant considering the assumptions and uncertainties inherent in the method of calculation.

Four significant and characteristic features of the alcohol spectra (Figure 6), observed in the hydroxyl-proton dilution–shift study, readily differentiate between the diastereomers and also shed additional light on their hydrogen-bonding abilities. First, the hydroxyl proton of the threo alcohol (I-OH) is strongly coupled with H-2 over the entire concentration range studied (0.009–0.235 *M*). The large coupling constant, J_{H^2COH} = 9.0 ± 0.3 Hz, was determined at a sweep width of 50 Hz and compares with larger values reported by Bauld and Rim[17] (12.5 Hz), Stolow and Gallo[19] (11.4 Hz) and Fraser and coworkers[20] (10.5 Hz). Second, the H-2 signal of I-OH is appropriately a very broad envelope, which collapses to a doublet of triplets upon addition of deuterium oxide (Figure 6). The magnitude and invariant nature of J_{H^2COH} over the 25-fold concentration range are evidence of a strong intramolecular hydrogen bond in the threo isomer. In contrast, the hydroxyl proton of the erythro alcohol (II-OH) is a distinct doublet ($J_{H^2COH} \cong$ 2–3 Hz) only at concentrations below 0.063 *M* (<0.005 mol fraction). Accordingly, H-2 is observed as a broadened "quartet" or overlapping doublet of triplets. Apparently at concentrations >0.06 *M*, internal association of the erythro alcohol is reduced by intermolecular association where proton exchange is more rapid, and thus the hydroxyl proton doublet collapses to a broad singlet.

Parallel behavior between the dihedral angle dependence of J_{HCOH} and the well-established dihedral angle–J_{HCCH} relationship[42] has been noted.[17,19,20,43,44] Fraser and coworkers[20] have evaluated the constants in the Karplus-type equation for J_{HCOH} from available experimental data (eq 8). If it is assumed that only

$$J_{HCOH} = 10.4 \cos^2 \phi - 1.5 \cos \phi + 0.2 \qquad (8)$$

intramolecularly hydrogen-bonded rotamers contribute to J_{HCOH}, then application of eq 8 to I-OH (J_{HCOH} = 9.0 Hz) and II-OH (J_{HCOH} = 2–3 Hz) gives dihedral angles ϕ_{HCOH}, of 148 and 110–118°, respectively. The calculated $\phi_{HCOH} = 148°$ for the threo alcohol is in excellent agreement with the value (155 ± 10°) obtained from a molecular model of rotamer Ic ($\phi_{2,3}$ = 65°). The calculated angle for the erythro alcohol (ϕ_{HCOH} = 110–118°) is intermediate between mea-

(41) For example, eclipsed conformers in butane are 3–6 kcal/mol less stable than staggered rotamers (E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, Chapter 6), and for the alcohols hydrogen bonding should contribute *ca.* 1.0 kcal/mol toward stabilization of rotamers Ic and IIc.[14]

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(43) C. P. Rader, *ibid.*, 88, 1713 (1966).
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sured values for rotamers IIc and IId; *i.e.*, nearer the angle ($\phi_{HCOH} \cong 115°$ where $\phi_{2,3} \cong 30°$) measured for a planar C_2–O–H···S–C_3 chelate ring.

The third distinguishing feature of the alcohol spectra (Figure 6) is the difference in coupling pattern of the methylene protons at C-1 with H-2. In these ABX systems the geminal couplings (J_{AB}) are large compared to the vicinal couplings (J_{AX} and J_{BX}) and to the small chemical-shift separations (δ_{AB}) thus leading to deceptively simple spectra.[45] In the threo alcohol [I-OH; $J_{1,1'} \cong -16$ Hz and $^1/_2(J_{1,2} + J_{1',2}) = 6.2$ Hz] two weak satellite bands are evident on the low-field side of the two major bands centered at τ 7.32 (Figure 6), the corresponding high-field satellites being buried beneath the H-4 multiplet. These satellite bands are more readily discernible in the spectrum of the threo acetate (I-OAc; see arrows in Figure 7). In the erythro alcohol or acetate (II-OH, Figure 6; II-OAc, Figure 7) only two lines are seen for H-1 and H-1' [$^1/_2(J_{1,2} + J_{1',2}) \cong 5.0$–$5.5$ Hz], which form the AA' part of an AA'X pattern (deceptive ABX) with H-2. These patterns are not modified significantly by either concentration or solvent changes.

The fourth major difference between the nmr spectra of the alcohols is the dilution behavior of the patterns for H-4 and H-5. At concentrations below 0.08 *M* the eight-line pattern for H-4 and H-5 of the erythro alcohol collapses to a doublet [Figure 6, $^1/_2(J_{3,4} + J_{3,5}) = 5.8$ Hz]. This AB → AA' transition results from a downfield dilution shift of H-5, and $\delta_{AB} \rightarrow 0$ at about the concentration (0.08 *M*) where chloroform has effectively eliminated intermolecular hydrogen bonding (ir data above). The eight-line pattern for H-4 and H-5 of the threo alcohol (I-OH) is insensitive to concentration changes. Furthermore, the spectra of both acetates (I-OAc and II-OAc, Figure 7) exhibit the eight-line patterns for H-4 and H-5 over this same concentration range. Apparently a specific interaction occurs between chloroform and the erythro alcohol, for which the hydroxyl group is necessary. That is, the resulting species does not involve interaction only between the episulfide ring and chloroform.

Solvent shifts of proton resonances induced by benzene due to specific complex formation have been extensively examined for many types of compounds,[46–51] but we know of no study of solvent shifts for episulfides. Shielding values ($\Delta^{C_6D_6}_{CCl_4}$) for protons of the threo (I-OAc) and erythro (II-OAc) acetates are positive and fall in the range 0.15–0.81 ppm (Table II). Similar, but smaller, shielding factors have been observed for epoxides[50] where a similar collision complex is likely. The nearly identical shielding of H-4 and H-5 in both episulfides suggests that benzene forms, with the dipole

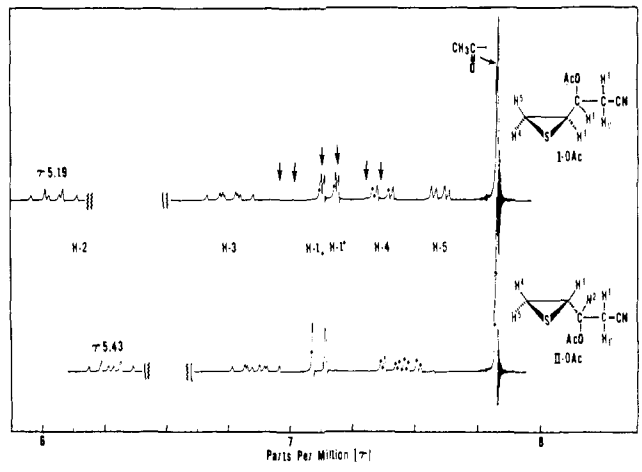

Figure 7. 100-MHz nmr spectra of acetoxy epithiobutanes in chloroform-*d* (0.5 *M*).

of the episulfide ring, a transient complex in which the planes of the two ring systems are approximately perpendicular.

Large shielding values for the acetate methyl (0.45–0.52) and cyanomethyl (0.67–0.81) protons signify strong benzene interactions with these highly polar groups also.

Experimental Section

Preparation and Purity of the Epithiobutanes (I and II). The episulfides (R = H) were obtained as previously reported.[3,4,7] The corresponding acetates (R = Ac) were prepared from the pure alcohols by acetylation with acetic anhydride in pyridine at 10°, followed by chromatography on silica gel (80–90%).[4,5] The alcohols and acetates were shown to be pure by ir and nmr spectra, and by gas–liquid (glc) and thin layer chromatography (tlc).[7] The model compound, (*S*)-1-cyano-2-hydroxy-3-butene, was obtained and its purity ascertained as previously reported.[4,7]

Ir and Nmr Spectra of the Epithiobutanes (I and II). The ir spectra of the alcohols (I and II, R = H) were obtained with a Perkin-Elmer Model 337 grating spectrophotometer.[52] A 1.0-cm sodium chloride cell was used for the carbon tetrachloride solutions, and concentrations were varied between 0.00166 and 0.03700 *M*. A 0.1-cm sodium chloride cell (matching reference) was used for the chloroform spectra with concentrations varied from 0.00797 to 0.08670 *M*. The temperature of the measurements was *ca.* 25°. Frequency measurements are believed good to better than ±5 cm^{-1}, and there was no change in frequency of either the free or associated band with dilution. Spectrograde carbon tetrachloride was used without further purification. Spectrograde chloroform for the ir and nmr studies was shaken with six portions of distilled water and dried over sodium sulfate, followed by passage through a silicic acid column. The nmr spectrum of purified chloroform showed that trace amounts of contaminants were removed by this treatment.

Nmr spectra were recorded on a Varian Associates HA-100 instrument and chemical shifts (τ) are given relative to internal tetramethylsilane (TMS) standard (Table II, Figures 6 and 7). Spectra of the four compounds (I and II, R = H, Ac) were recorded in chloroform-*d* on 0.0094–0.93 *M* solutions at an operating temperature of 31° and sweep widths of 50–250 Hz. Only H-4 and H-5 of the erythro alcohol (II-OH) and the hydroxyl protons of both episulfides were significantly affected by concentration changes. The chemical shift of the hydroxyl proton of each alcohol

(45) This interpretation is the result of helpful comments and calculations given by a referee (Dr. G. Slomp), whom we acknowledge with pleasure. For discussions of deceptively simple ABX spectra see: R. J. Abraham and H. J. Bernstein, *Can. J. Chem.*, **39**, 216 (1961), and C. N. Banwell in "Nuclear Magnetic Resonance for Organic Chemists," D. W. Mathieson, Ed., Academic Press, New York, N. Y., 1967, Chapter 6.

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(52) Mention of firm names or trade products does not constitute endorsement by the U. S. Department of Agriculture over firms or similar products not mentioned.

was determined as a function of concentration [(0.94 − 25.16) × 10^{-2} M] relative to the chloroform signal at τ 2.73 (727 Hz downfield from TMS) (Figure 4). The spectra of the acetates (I and II, R = Ac) also were obtained in carbon tetrachloride and benzene-d_6 (0.50–0.93 M). In general, all spectra were recorded under identical conditions and were reproducible. Chemical shifts and coupling constants were determined either from first-order analyses or from appropriate ABX approximations.[53]

(53) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, N. Y., 1959, Chapter 6.

Nuclear Magnetic Resonance Determination of Ketone Basicity and the Use of Ketones as Indicators for Evaluation of Medium Acidity

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Abstract: Basicity constants determined by proton nmr are reported for several types of ketones. Carbonyl substituent chemical shifts are plotted against Hammett acidity (H_0) yielding half-protonation values that reproduce spectrophotometric basicity constants. The nmr method facilitates basicity measurements for extremely weak ketone bases in superacid media. Basicity constants for several α-halogen substituted acetones are reported. Fluoro, chloro, and bromo substituents all reduce ketone basicity substantially. The three halogens are approximately equal in their effect. Carbonyl compounds that are not stable enough for spectrophotometric basicity studies may be evaluated by nmr. The nmr basicity constant for acetaldehyde (pK = −10.2) indicates that the aldehyde is far less basic than expected. Several ketones are used as a set of indicators for rapid evaluation of (Hammett) medium acidity by nmr. Applicability of the nmr method for acidity evaluation over the entire Hammett scale (currently H_0 = 0 to −17.5) allows facile measurements in both superacid and conventional acid systems.

The quantitative study of ketones as weak organic bases has occupied various groups of chemists during the past decade. A review article by Arnett, published in 1963, gives an excellent account of the earlier work.[1] Ketone basicity values published since 1963 have primarily been reevaluations and interpretations of the earlier results.

In the last few years, it has been shown that ketones do not behave as true Hammett bases[2] and that the pK_a values reported in earlier investigations were not actually thermodynamically defined constants but, instead H_0 acidity values for half-protonation. Nevertheless, it has been shown that useful correlations of these half-protonation basicity values with other reactivity parameters exist for various structurally related bases.[3] For ketone bases the observed deviations from ideal Hammett behavior are due in part to the hydrogen-bonding interactions of ketones in the acid media.

The usual experimental method employed for measurement of ketone basicity constants is spectrophotometric, utilizing visible and/or ultraviolet absorptions of the protonated and unprotonated base.[4,5] Difficulties often arise in separating the affects of protonation and hydrogen bonding on the observed spectra.[1,2,5]

Nuclear magnetic resonance has been utillized in a few instances for basicity determinations.[6,7] Taft studied fluorine magnetic resonance of *para*-fluorinated aryl bases in acid media.[6] His method was limited by the choice of fluorinated bases and solubility considerations. Deno reported a pK[8] value for acetone using the proton nmr chemical shift of the methyl group relative to the resonance of external benzene.[7] Proton nmr has been used in several attempts to determine basicity constants for amides, alcohols, and ethers.[7,9,10] These attempts were quantitatively unsuccessful due to the relatively large effect of hydrogen bonding (between the protonated base and the medium) on the nmr chemical shifts studied.

In this paper, a proton nmr method will be presented and substantiated with nmr determined basicity constants for ketones of known basicity. This method allows basicity determinations for ketones that have not previously been studied: for example, α-halo ketones.[11] In addition, ketone systems of limited stability can be investigated.

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