Intramolecular Hydrogen Bonding in Some Aliphatic α- and β-Hydroxy-carboxylates

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High resolution proton magnetic resonance (NMR) spectroscopy has recently been employed as a powerful means for investigating various types of hydrogen bonds. It is useful when the changes in the chemical shift of a proton involved in the formation of a hydrogen bond are sufficiently large,$^{1)}$ and it is useful as an indicator of hydrogen-bond formation similar to the changes in X–H stretching frequency due to the formation of a hydrogen bond.$^{2)}$

The formation of intramolecular hydrogen bonds in dilute solutions in non-polar solvents is a simple case, since in general only one species is involved. For various *o*-substituted phenols in carbon tetrachloride, the change in the chemical shift of the hydroxyl-proton due to the formation of an intramolecular hydrogen bond has been correlated with the corresponding change in the O–H stretching frequency.$^{3,4)}$ In addition, the dilution-shift curves of *o*-halophenols$^{4,5)}$ in carbon tetrachloride, quite different from that of phenol itself, are generally of an s-shape, with a reversal of the curvature at a relatively high concentration.

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1) J. A. Pople, W. G. Schneider and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., New York, N. Y. (1959), p. 400.

2) G. C. Pimental and A. L. McClellan, "The Hydrogen Bond," W. H. Freeman and Co., San Francisco (1960), p. 142.

3) A. L. Porte, H. S. Gutowsky and I. M. Hunsbenger, *J. Am. Chem. Soc.*, **82**, 5057 (1960); J. R. Merrill, *J. Phys. Chem.*, **65**, 2023 (1961).

4) L. W. Reeves, *Can. J. Chem.*, **38**, 736 (1960); L. W. Reeves, E. A. Allan and K. O. Strømme. ibid., **38**, 1249 (1960); E. A. Allan and L. W. Reeves, *J. Phys. Chem.*, **66**, 613 (1962).

5) C. M. Huggins, G. C. Pimental and J. N. Shoolery, ibid., **60**, 1311 (1956).

The intramolecular hydrogen bonding in some aliphatic α- and β-hydroxy-carboxylates, particularly *d*-tartrates, has previously been studied by means of optical rotation6) and by infrared spectroscopy.7) The present paper will report on further investigation of the esters carried out by NMR and infrared spectroscopy.

Experimental

All ethyl esters were prepared by Fischer's method from hydroxy-carboxylic acids and ethyl alcohol in the presence of dry hydrogen chloride and were repeatedly fractionated. These esters are of the racemic form, unless otherwise stated, and are listed in Table I.

All the NMR spectra of the esters were measured in pure liquid or in solutions in varions concentrations up to 0.002 mol./l. in carbon tetrachloride at 20°C with a Varian Model DP 60 NMR spectrometer; chemical shifts were read by the sideband method, using tetramethylsilane (TMS) as an internal standard. Each shift in the table is the average of at least two independent measurements. Full analysis of the signals in the spectra could readily be made on the basis of the chemical shift and the relative intensity.

Many data of the infrared measurement were taken from the previous works,7) while others were obtained in a similar manner at 20°C; the pure liquid measurement, however, was carried out with a Hitachi EPI-002 infrared spectrometer equipped with a sodium chloride prism and the solution measurement, with a Perkin-Elmer 21 spectrometer equipped with a lithium fluoride prism. The infrared and the NMR data obtained for the hydroxyl groups in the esters are shown in Table I.

Results and Discussion

Infrared Measurements of the Hydroxyl Groups. — The infrared spectra of the pure liquid esters display in each case one broad absorption band at a frequency of from 3420 to 3500 cm^{-1}, higher than the 3350 cm^{-1} of the hydroxyl in pure ethanol, as seen in Table I.

TABLE I. CHEMICAL SHIFTS AND FREQUENCIES OF HYDROXYL GROUPS

	Ethyl ester	B. p. °C/mmHg	Chemical shift $-\delta_{OH}$, c.p.s. from TMS			Frequency (ν_{OH}, cm^{-1})		
			δ_1[a]	δ_0[b]	$\Delta\delta$	ν_1[a]	ν_0[c]	$\Delta\nu$
I	Glycolate	75.0/35	267	103	164	3427	3545 (st) 3611 (w)	118
II	Lactate	72.5/37	259	126	133	3436	3543 (st) 3613 (w)	107
III	α-Hydroxyisobutyrate	65.5/31	238	145	93	3478	3544 (st) 3606 (w)	66
IV	β-Hydroxypropionate	79/12	250	85	166	3426	3582 (st) 3625 (sh)	156
V	β-Hydroxybutyrate	78/12	247	116	131	3430	3560 (st) 3625 (sh)	130
VI	Malate	144/24.3	246	137	109	3441	3535 (st) 3590 (sh)	94
VII	*d*-Tartrate	156.5/12	248	143	107	3454	3532 (st) 3588 (w)	78
VIII	*meso*-Tartrate	156/13.5 M. p. 58°C	—	145	—	—	3534 (st) 3584 (sh)	—
IX	*cis*-Hexahydrosalicylate	91.5/5	214	138	76	3494	3540 (st)	43
X	*trans*-Hexahydrosalicylate	92/3.5	237	124	113	3474	3560 (st) 3593 (st)	86
	α-Methoxypropionate	90/138						
	Methanol[d]		295	29	266			
	Ethanol[d]		320	42	278	3350	3631	281
	Isopropanol[d]		306	50	256			
	t-Butanol[d]		283	48	235			

a) Value for pure liquid.

b) Value extrapolated to infinite dilution in CCl$_4$.

c) Value at a concentration of ca. 0.02∼0.04 mol./l. in CCl$_4$. "st" means a strong band, "w" a weak band and "sh" a shoulder.

d) The reported values in J. C. Davis, K. S. Pitzer and C. N. Rao, *J. Phys. Chem.*, **64**, 1744 (1960) were converted from Me-peak to TMS as standard.

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6) T. M. Lowry and J. O. Cutter, *J. Chem. Soc.*, **121**, 532 (1925); W. Kauzmann and H. Eyring, *J. Chem. Phys.*, **9**, 41 (1941); Y. Tsuzuki, *J. Chem. Soc. Japan*, *Pure Chem. Sec.* (*Nippon Kagaku Kwaisi*), **64**, 282, 290 (1943).

7) a) Y. Tsuzuki et al., ibid., **75**, 1030, 1033 (1954); b) N. Mori, Y. Tsuzuki and Tsubomura, ibid., **77**, 459 (1956).

Of particular interest is the steric effect of the methyl group on the O–H frequency. The OH frequency of the α-hydroxy-esters increases in the order of the glycolate (3427 cm^{-1}), the lactate (3436 cm^{-1}) and the α-hydroxy-isobutyrate (3478 cm^{-1}) ; in the β-hydroxy- esters a similar trend is found for the β-hydroxypropionate (3426 cm^{-1}) and the β-hydroxybutyrate (3430 cm^{-1}). This is undoubtedly to be attributed to a weaker intermolecular hydrogen bond resulting from steric hindrance by the methyl group.

Preliminary measurements of the lactate and the tartrate carried out in concentrations of up to ca. 0.002 mol./l. have shown that the position of the O–H band is displaced with a decreasing concentration towards a higher frequency and that, simultaneously, a shoulder or an additional weak band appears, overlapped with the first strong band. At different concentrations below ca. 0.05 mol./l., the positions and relative intensities of the bands were substantially independent of the concentration. Accordingly, the spectra of the other esters were measured in a concentration near 0.03 mol./l. in carbon tetrachloride. The results of the measurement in solution are shown in Figs. 1—5.

In the α-hydroxy-esters, the strong and the weak bands appear at ca. 3545 and 3610 cm^{-1} respectively. The former should be assigned to the hydroxyl group intramolecularly associated with the carbonyl in the carboxylate

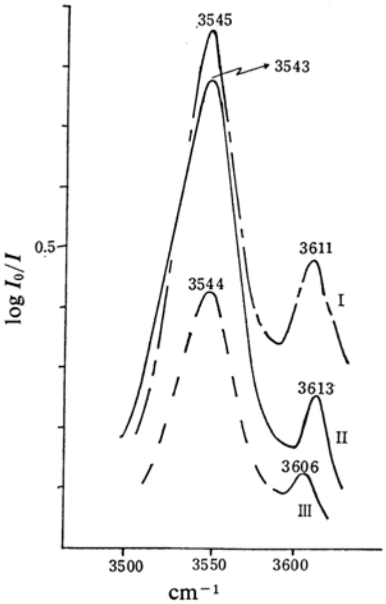


Fig. 1. IR spectra of hydroxyl groups in CCl_4.
I Ethyl glycolate, 0.002 mol./l., 30 mm. cell
II Ethyl lactate, 0.004 mol./l., 31 mm. cell
III Ethyl α-hydroxyisobutyrate, 0.002 mol./l., 30 mm. cell

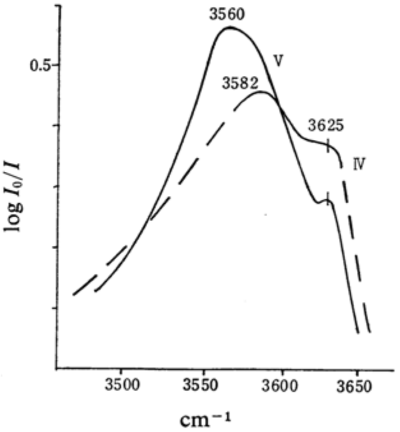


Fig. 2. IR spectra of hydroxyl groups in CCl_4.
IV Ethyl β-hydroxypropionate, 0.04 mol./l., 3 mm. cell
V Ethyl β-hydroxybutyrate, 0.046 mol./l., 3 mm. cell.

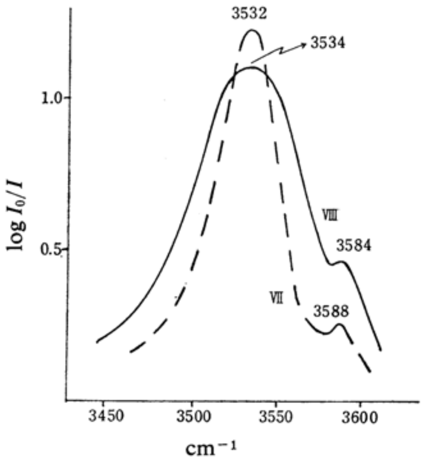


Fig. 3. IR spectra of hydroxyl groups in CCl_4.
VII Ethyl *d*-tartrate, 0.030 mol./l., 3 mm. cell
VIII Ethyl *meso*-tartrate, 0.010 mol./l., 30 mm. cell

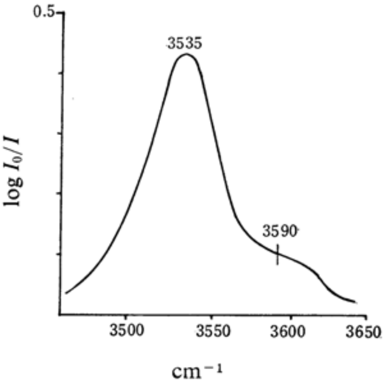


Fig. 4. IR spectrum of the hydroxyl group in ethyl malate in 0.026 mol./l. in CCl_4. (3 mm. cell).

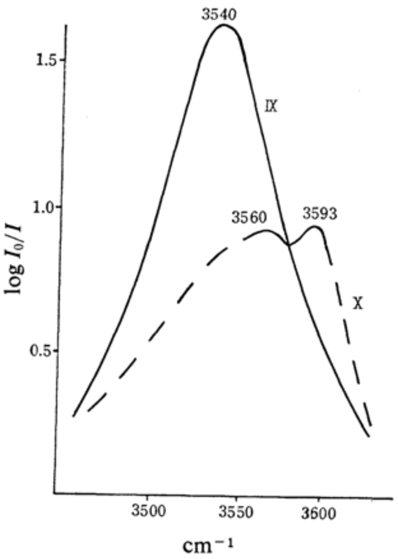
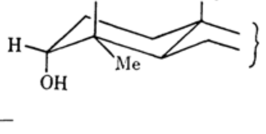


Fig. 5. IR spectra of hydroxyl groups in CCl_4.
IX Ethyl *cis*-hexahydrosalicylate, 0.03 mol./l., 30 mm. cell
X Ethyl *trans*-hexahydrosalicylate, 0.03 mol./l., 30 mm. cell.

group, as has been suggested in a previous paper.[7b)] On the other hand, the latter is considerably lower than the 3631 cm^{-1} of the free hydroxyl of ethanol, although near that (3580~3610 cm^{-1}) of the intramolecularly hydrogen-bonded hydroxyl in many aliphatic diols.[8)] Nevertheless, it is not evident whether the weak band is due to the hydroxyl associated with the ether-oxygen in the carboxylate group or to the free hydroxyl, because the electron-attracting nature of the carboxylate group would cause the absorption band of the α-hydroxyl to shift towards a lower frequency.

In all the β-hydroxy-esters except the isomeric hexahydrosalicylates, the strong band appears at 3560 or 3582 cm^{-1}; this is due to the hydroxyl intramolecularly associated with the carbonyl in the carboxylate group. The weak band at 3625 cm^{-1} may be due to the hydroxyl, either free or associated in a manner similar to that in the corresponding case of the α-hydroxy-esters. This may be compared with the 3630 cm^{-1} of the free hydroxyl in methyl 3-hydroxyurs-12-en-24-oate:[9)]



Further, when the frequencies of the hydroxyls in the α- and β-hydroxy-esters in a liquid (ν_1) and in a dilute solution (ν_0) are compared, the values of ν_0 for the strong band due to the α-hydroxyl are seen to be lower by 15~30 cm^{-1} than those for the β-hydroxyl; an even more remarkable difference is found in the values of $\nu_0-\nu_1$ or $\Delta\nu$. Consequently, this seems to be directly related to the strength of the intramolecular hydrogen bond in the α- and β-hydroxy-esters, which form a five- and a six-membered ring respectively. It is also of interest that, as the number of methyl groups on the carbon atom with the hydroxyl group increases, the frequencies of both the weak and the strong bands decrease and there is a simultaneous decrease in the intensity of the former band relative to that of the latter, as can be seen in Figs. 1 and 2. However, this is not surprising, since the methyl group would bring about a geometry faborable to form a stronger intramolecular hydrogen bond. Similarly, in isomeric ethyl hexahydrosalicylates, the intramolecular hydrogen bond of the hydroxyl formed with the carbonyl in the cis form is considered to be stronger than that of the trans form.

Chemical Shifts of Hydroxyl-protons and Other Protons.—As may be seen in Table I, the signal position (δ_1) of the hydroxyl-proton in each of the α- and β-hydroxy-esters in the pure liquid state moves towards a higher field with the increasing number of methyl groups on the carbon atom with the hydroxyl group. Such a trend is also seen in the series of alcohols except methanol, as may be seen in the table. This is undoubtedly due to a weaker intermolecular hydrogen bond resulting from steric hindrance by the methyl group, as has been pointed out in connection with the infrared measurement. Figure 6 shows the dilution-shift curves for some of the esters investigated. The insert in the figure, plotted on a larger scale, shows the detailed low-concentration measurements extrapolated to infinite dilution. The chemical shifts (δ_0) of the hydroxyl-protons in the table are those extrapolated to infinite dilution. It is of interest that the value of δ_0 in each of the α- and β-hydroxy-esters increases with the increased number of methyl groups on the carbon atom having the hydroxyl group, although no such trend is seen in the series of alcohols except methanol. Consequently, this must be related to the intramolecular hydrogen-bonding strength in the esters.

It is known that a stronger intramolecular hydrogen bond results in a lower value of the dilution shift, as may be seen, for example, in *o*-chlorophenol[5)] in a carbon tetrachloride

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8) L. P. Kuhn, *J. Am. Chem. Soc.*, **74**, 2492 (1952).

9) A. R. H. Cole and G. T. A. Müller, *J. Chem. Soc.*, **1959**, 1224.

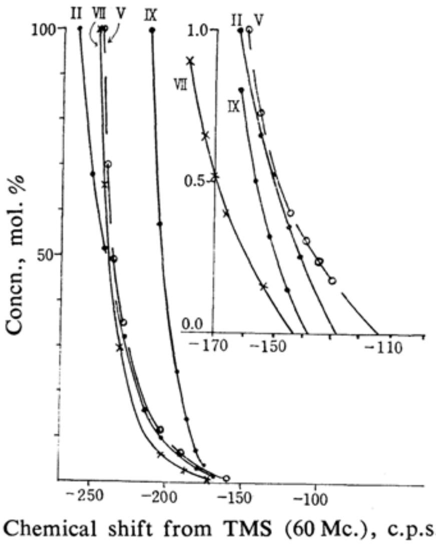

Fig. 6. Changes in chemical shifts of hydroxyl protons in CCl_4. The numbers on the figure refer to the numbered compounds in Table I.

solution, where the dilution shift of the hydroxyl-proton is only 0.8 p.p.m. as compared with 2.8 p.p.m. of the phenols containing no intramolecular hydrogen bond; also, in β-chloroethanols[10] the value is 3.5 p.p.m., which is lower than the 4.5 p.p.m. of ethanol itself. Accordingly, the relatively low dilution shifts of 1.3∼2.8 p.p.m. of the hydroxyl-protons in the esters are substantially caused by the intramolecular hydrogen bond formed in them. However, the curves of the dilution shifts for the esters, as shown in Fig. 6, are generally of an L-shape, differnt from that of *o*-chlorophenol, which features the reversal of the curvature at ca. 20 mol. % in carbon tetrachloride.[5] A similar reversal of curvature was observed even with ethanol itself at a low concentration of 1.5 mol. %[11] and also with some alcohols.[10] This might seem to lead to the conclusion that, even in a concentration as low as 1 mol. % (or ca. 0.01 mol./l.) or below, each of the esters consists of a system of monomers and intermolecularly associated species, with a decreasing proportion of the latter to the former on further dilution. This is strikingly different from the findings based on the infrared measurement of the hydroxyl group in a dilute solution, where substantially all molecules are present as monomer even in a concentration as high as 0.1 mol./l. This contradiction may be settled by a possible assumption that the changes in the chemical shift of the hydroxyl-proton

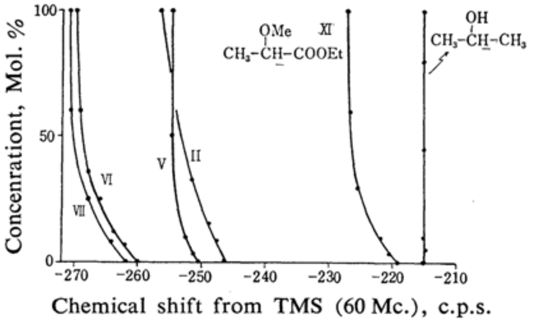

Fig. 7. Dilution shifts for the proton on a carbon atom having a hydroxyl group in CCl_4. The numbers on the figure refer to the numbered compounds in Table I.

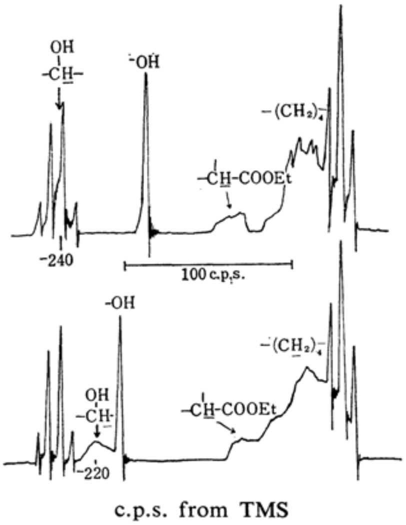

Fig. 8. NMR spectra of isomeric hexahydrosalicylates in CCl_4 (20 mol. %) at 60 Mc.
IX *cis*-Isomer
X *trans*-Isomer

on dilution are caused not only by the dissociation of the polymer, but also partially by some other factors such as those which would bring about the dilution shifts of protons other than the hydroxyl-proton, as will be mentioned later. Consequently, a dilution-shift curve of the hydroxyl-proton resulting from such factors would be superimposed on a real hydrogen-bond-shift curve of the proton to produce the dilution-shift curve of an apparent L-shape without the reversal of curvature.

In all the esters investigated, a similar dilution shift has also been observed for protons other than the hydroxyl-proton, most especially for the proton on the carbon atom with the hydroxyl group. The changes in the chemical shift of such protons in some of the esters are shown in Fig. 7. In general, the dilution shift of the proton on the carbon atom with

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10) T. M. Conner and C. Reid, *J. Mol. Spectroscopy*, **7**, 32 (1961).

11) E. D. Becker, U. Liddle and J. N. Shoolery, ibid., **2**, 1 (1958).

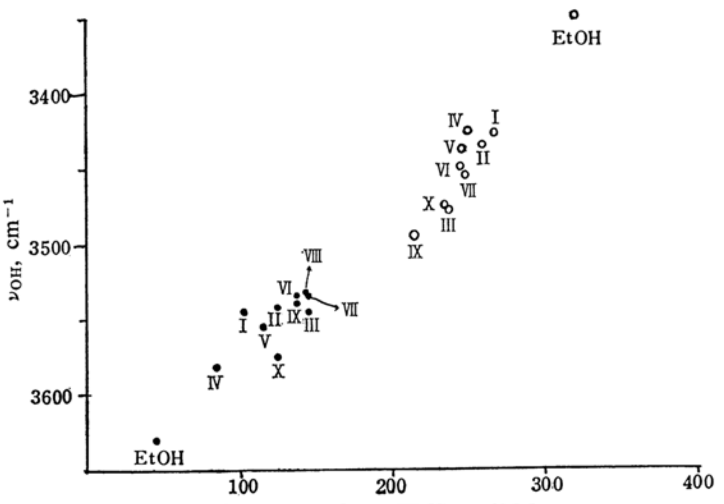
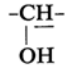


Fig. 9. Correlation of the chemical shift (δ_{OH}) with the frequency (ν_{OH}). The numbered points on the figure refer to the numbered compounds in Table I.
○ Pure liguid ● Infinitely diluted solution in CCl_4

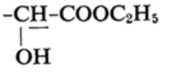
either the hydroxyl or carboxylate group, A or B, is ca. 5 c. p. s. towards a higher field, while that of the proton on the carbon atom with both groups C is ca. 10 c.p.s. in the same direction. Further, the signals due to the methyl- and methylene-protons in the ethylcarboxylate group shift by 3 c.p.s. towards a lower field. These shifts seem to have no direct relation to the hydrogen bonding, since there is a shift of 8 c.p.s. for the α-proton in ethyl α-methoxypropionate, but no shift for the α-proton in isopropanol.


$-\underline{CH}(OH)-$

(A)

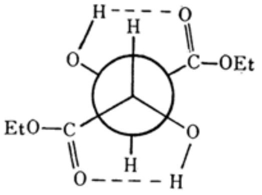
$-\underline{CH_2}-COOC_2H_5$

(B)

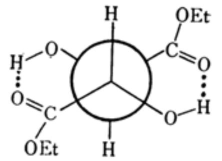

$-\underline{CH}(OH)-COOC_2H_5$

(C)

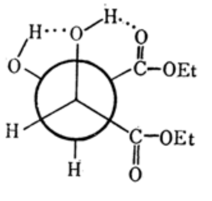
Intramolecular Hydrogen Bonding in Ethyl Tartrates, Malate and Isomeric Hexahydrosalicylates.—*Ethyl meso-Tartrate.*—The infrared spectrum of ethyl *meso*-tartrate in Fig. 3 displays on strong absorption band at 3534 cm^{-1}, with a shoulder at 3584 cm^{-1}; the relative intensity of the former to the latter is ca. 10. As for the form of the intramolecular hydrogen bonding of this ester in a dilute solution in carbon tetrachloride, conformation I seems to be the most preferable of the three I—III given below. This suggestion is based on the facts that the frequency of the strong band is very close to that of the α-hydroxyl group, especially in ethyl lactate and α-hydroxyisobutyrate, but it is almost completely different from those of the β-hydroxyl group and some diols. Furthermore, the chemical shift of the hydroxyl-proton in infinite dilution is substantially equal to those of the α-hydroxy-esters, but quite different from those of the β-hydroxy-esters. On the other hand, the shoulder seems to be due to the hydroxyl associated with the carbonyl in the β-carboxylate group in the same molecule. Conformation III, containing a hydrogen bond between the two hydroxyls, is unlikely, at least in a carbon tetrachloride solution, because of the relatively high steric repulsion between the groups in the conformation.



I

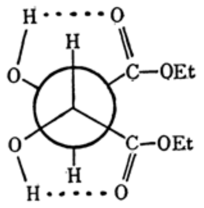


II

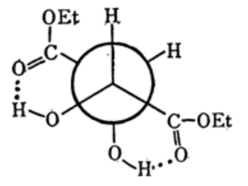


III

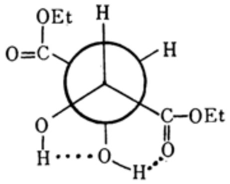
Ethyl d-Tartrate.—The infrared spectrum of this ester in Fig. 3 contains two bands, at 3532 and 3588 cm^{-1}, the relative intensity of the former to the latter being ca. 10. The frequencies of the bands and also the chemical shift in infinite dilution are the same as those of ethyl *meso*-tartrate; therefore, the strong band should be assigned to the hydroxyl associated with the α-carboxylate-carbonyl in conformation IV, as has been suggested in a previous paper.[7b] It is not evident whether or not the weak band is due to the hydroxyl in conformation V or VI.



IV



V

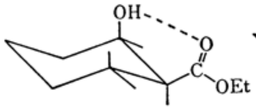


VI

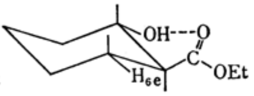
Ethyl Malate.—The strong band at 3535 cm^{-1} in Fig. 4 may be assigned to the hydroxyl forming the same type of intramolecular hydrogen bond as in the α-hydroxy-esters. This assignment is borne out by almost the same chemical shift of the hydroxyl-proton as that of the tartrates. The shoulder near 3590 cm^{-1} may be due to the hydroxyl associated with the β-carboxylate-carbonyl.

Ethyl cis- and trans-Hexahydrosalicylates.—According to the NMR spectra (60 Mc.) of isomeric 4-*t*-butylcyclohexanols[12] and decalols[13], the axial hydrogen on the carbon atom with the hydroxyl group appears in a field higher by ca. 30 c.p.s. than the signal position of the epimeric equatorial hydrogen (−235 c.p.s. from TMS), the two signals being broadened unresolved spin-spin multiplets. This fact is useful in the conformational analysis of the isomeric ethyl hexahydrosalicylates.

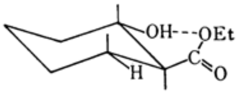
The NMR spectrum of the cis form in carbon tetrachloride in Fig. 8-IX displays a signal at ca. −240 c.p.s. overlapped with that of the methylene protons in the ethylcarboxylate group. On the other hand, the spectrum of the trans form in Fig. 8-X has a broadened signal at ca. −220 c.p.s. The infrared spectrum of the cis ester in Fig. 5 has only one strong absorption band, at 3450 cm^{-1}; consequently, conformation VII, containing an intramolecular hydrogen bond of the axial hydroxyl with the carbonyl in the equatorial carboxylate group, shold be assigned for this isomer. On the other hand, the infrared spectrum of the trans form in Fig. 5 contains two bands at 3560 and 3593 cm^{-1} with the intensity ratio of ca. 3 : 1. The former may be due to the hydroxyl associated with the carbonyl in conformation VIII, and the latter, to one associated with the ether-oxygen in conformation IX.



VII



VIII



IX

The Correlation between Chemical Shifts and Frequencies.—For various *o*-substituted phenols in a dilute solution in carbon tetrachloride, the change in the chemical shift of the hydroxyl-proton on the formation of an intramolecular hydrogen bond has been correlated with the corresponding change in the O–H stretching frequency.[3,4] Gränacher reported a similar correlation for intermolecular hydrogen bonds.[14] In the present work, the chemical shifts of the hydroxyl-proton of the hydroxy-ester in the pure liquid state and in infinite dilution in carbon tetrachloride have been correlated with the stretching frequencies of the O–H band in the respective states. Figure 9 shows graphically the correlation between the above two parameters for all the esters studied as well as for ethanol for the purpose of comparison. All plots of the chemical shifts against the frequencies lie roughly on a straight line between the plots for ethanol in the liquid state and in infinite dilution.

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[12] A. H. Lewin and S. Winstein, *J. Am. Chem. Soc.*, **84**, 2464 (1952).

[13] J. I. Musher, ibid., **83**, 1146 (1961).

[14] I. Gränacher, *Helv. Phys. Acta*, **34**, 272 (1961).