Tetrahedron Vol. 25, pp. 3609 to 3616. Pergamon Press 1969. Printed in Great Britain

INFRARED STUDIES WITH TERPENOID COMPOUNDS—V[1,2]

INTERMOLECULAR HYDROGEN BONDING OF VARIOUS DIHYDROXY AND TRIHYDROXY CHOLANE DERIVATES AND RELATED COMPOUNDS

S. KOVAC

The Institute of Organic Chemistry, Slovak Technical University, Bratislava, Czechoslovakia

and

G. EGLINTON*

The Chemistry Department, Glasgow University, Glasgow, Scotland

(*Received in the UK* 14 *March* 1969; *Accepted for publication* 17 *April* 1969)

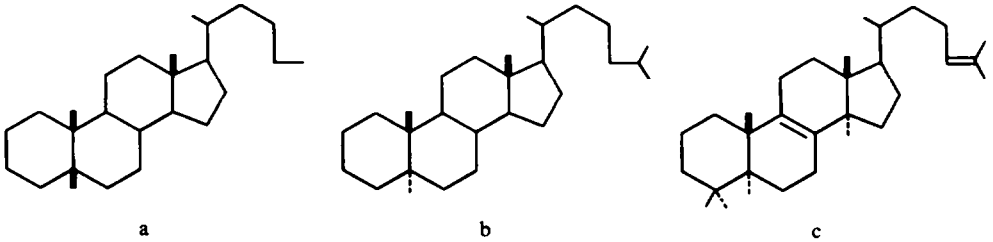
Abstract—Unusually persistent self-association in solution has been observed for some dihydroxy- and trihydroxy-cholane derivates and related compounds bearing hydroxyls in α-positions of the steroidal skeleton. In mixtures of dihydroxy steroids examined with dibasic compounds as diketo steroids or some diamines in carbon tetrachloride only a weak association was observed.

IT IS frequently assumed that self-association is absent at concentrations as low as 10 mM except in special cases, such as carboxylic acids,[3] oximes and dimedone derivatives,[4,5] cyclohexane-1,3-diols,[6,7] steroidal hydroxyesters,[7] labdane-8α, 15-diol,[8] novolaks(bisphenylol alkanes),[9] 3-acetyl-5-hydroxybenzo-(b)-thiophen,[10] 5β-B-norcholestane-3α-6α-diol[11] and certain substituted phenols.[12,13]

It is known that 3α,12α-dihydroxycholanic acids form clathrate complexes, called choleic acids, with a wide variety of organic compounds.[14–17]

Di- and trihydroxysteroids could behave in a similar fashion, and a wide range of polyhydroxy steroids are known in which the rigid tetracyclic skeleton offers an almost ideal molecular framework for studies directed towards the stereochemical aspects of H-bonding between molecules.

We have examined cholane (**a**), cholestane (**b**) and polyporanate (**c**) types of steroids:



a b c

* Present address: Chemistry Department, Bristol University, Bristol, England.

3α,12α-Dihydroxy methyl cholanate (I)
3α,7α-Dihydroxy methyl cholanate (II)
12α,24-Dihydroxy-5β-cholane (III)
7α,24-Dihydroxy-5β-cholane (IV)
3α,7α,24-Trihydroxy,5β-cholane (V)
3α,12α,24-Trihydroxy-5β-cholane (VI)
3α,7α12α-Trihydroxy methyl cholanate (VII)
7α,12α-Dihydroxy-5β-cholane (VIII)
3α,7α,12α-Trihydroxy-5β-cholestane (IX)
Methyl polyporanate (X)
Methyl isopolyporanate (XI)
3β,7β-Dihydroxy-5α-cholestane (XII)
3α,7α12α,24-Tetrahydroxy-5β-cholane (XIII)

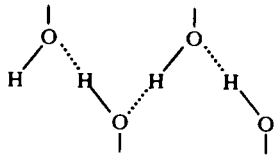
To study the association of dihydroxy steroids with diketo steroids or other dibasic compounds we used these compounds:

3,12-Dioxo-5α-cholane (XIV)
7,12-Dioxo-5β-cholane (XV)
3,12-Dioxo-5β-cholane (XVI)
camphoquinone (XVII)
N,N′-Tetramethyl-hexamethylene diamine (XVIII)
1,2-2-pyridyl-ethene (XIX)
1,2-2-pyridyl-ethane (XX)

RESULTS AND DISCUSSION

IR spectral data of the compounds investigated (Tables 1 and 2), reveal that a strong self-association is present only in dihydroxy and trihydroxy-5β-steroids containing OH groups in α-positions of the steroidal skeleton (I, II, VII, VIII and IX). All these compounds self-associate down to very low concentrations. Thus, progressive dilutions from 50 to 0·3 mM (I); from 33 to 0·76 mM (II); from 26·8 to 0·225 mm (VII) and from 10·59 to 0·557 mM (IX), clearly show (Table 1), absorptions at 3415–3450 cm^{-1} in CCl_4 due to an intermolecular H-bonding (bands are concentrations-dependent). The self-association is stronger with trihydroxy-5β-steroids (VII and IX) than with dihydroxy-5β-steroids (I, I II and VIII), (Table 1). It further follows from data listed in Table 1, that dihydroxy-5β-steroids bearing the OH groups in 7α, 12α (VIII) or in 3α, 12α (I)-positions, associate more strongly than does 3α, 7α-dihydroxymethyl cholanate (II).

The simplest way in which the IR spectral data of the dihydroxy-5β-steroids investigated may be accommodated would be an interlocking system of H-bonds, hydroxyls from one molecule alternating with those from another.



This as well as examination of Dreiding models suggests that clusters of molecules such as those of compounds I and VIII can be assembled with the polar α-faces bearing the rigidly oriented OH groups facing inwards and the nonpolar β-faces turned outwards. Within such a cluster unstrained arrangements involving energetically favoured sequences of interlocked H-bonds are possible.

In the case of other dihydroxy-5β-steroids studied this type of association is impossible because of the closer proximity of the OH groups (see the distances between the two O atoms of both hydroxyls, determined on Dreiding models, Table 1).

The precise nature of the associated species, however, cannot be decided from these data alone. At the concentrations employed higher oligomers, though unlikely, may still be members of the association equilibrium.

Compounds VII and IX, showing abnormally persistent association at very low concentrations, probably exist as "dimers", clustering into tetramers and, possibly, higher oligomers at somewhat higher concentrations. These compounds can be associated in a similar way as pointed out with dihydroxy-5β-steroids (see above). As a result of the large $O_3 \cdots O_7$, $O_7 \cdots O_{12}$, $O_3 \cdots O_{12}$ distances, intramolecular H-bonding within a single molecule is not possible (Table 1).

It is very difficult to visualize the dispositions of the molecules in such clusters. Probably, the cluster of four molecules (A, B, C, D) of compounds VII or IX (Table 1), is so arranged that the three hydroxyls (positions 3α, 7α, 12α) of each molecule form two chains of interlocking intermolecular H-bonds. In such a cluster two hydroxyls (position 12α (A) and position 7α (D) remain free:

$$A_{7\alpha} \cdots B_{7\alpha} \cdots A_{3\alpha} \cdots B_{12\alpha} \cdots C_{3\alpha} \cdots D_{12\alpha}$$
$$A_{12\alpha} \cdots B_{3\alpha} \cdots C_{12\alpha} \cdots D_{3\alpha} \cdots C_{7\alpha} \cdots D_{7\alpha}$$

It is interesting that carbonyl groups in the side chain of the hydroxy steroids studied (I, II, VII) play only a minor role in the association, but do become involved in H-bonding at the higher concentrations (shoulder at 1719 cm^{-1}, Table 1). However, the presence of the carbonyl group in the side chain of compound VII causes stronger association in comparison with compound IX (Table 1).

The centre of the absorption band of the associated hydroxyls shifts to lower frequencies as the concentration in increased; thus, there is a 52 cm^{-1} and a 40 cm^{-1} shift downwards when solutions of VII and I, respectively, are compared in the range of concentrations examined.

The relatively high solubility of compounds I, II, VII and IX in carbon tetrachloride, would result from the utilization of the hydroxyls in cluster formation.

There is a marked decrease of the strength of association on passing from carbon tetrachloride to chloroform solution with the expected lowering in frequency and increase in breadth of the bands of the free OH and CO groups.

It is very surprising that at the concentration of 3·045 mM self-association of VII still exists in chloroform; this is a unique case of abnormally strong intermolecular H-bonding.

Osmometric data for apparent molecular weights in carbon tetrachloride solution of compounds I, II, VII and IX are in accord with the IR spectral data. Thus, there is a difference in the degree of association of IX and VII. The ester group (VII) results in a steeper association curve (Fig. 2).

TABLE 1. HYDROXYL AND CARBONYL ABSORPTIONS OF HYDROXYSTEROIDS IN CCl_4

Compound No.	Distance $O_x \cdots O_y$ Å	Conc (mM)	Cell path (mm)	νOH						Cell path (mm)	νCO			K
				Free			Bonded							
				ν	$\Delta\nu_{\frac{1}{2}}$	ε_a	ν	$\Delta\nu_{\frac{1}{2}}$	ε_a		ν	$\Delta\nu_{\frac{1}{2}}$	ε_a	
I	5·2	50	0·51	3622	(29)	20	3415	275	135	0·11	1742[c]	18	575	
		8·4	2·0	3624	28	85	3455	250	65	1·0	1742	18	580	813 ± 20
		0·3	60·0	3624	28	125	(3455)	—	(10)	20·0	1742	17	580	
II		33	1·0	3624	(32)	45	3415	270	80	0·11	1741[c]	17	585	
	4·2	5·08	5·0	3625	27	100	3415	—	25	1·0	1741	18	580	183 ± 30
		0·76	20·0	3625	27	115	(3415)	—	(10)	5·0	1741	17	585	
III	9·7 (max) 3·6 (min)	10	5·0	3628	22	105	(3472)	—	(10)					
IV	9·8 (max) 5·0 (min)	10	5·0	3629	22	115	(3472)	—	(10)					
V	$O_3 \cdots O_7$–4·2	35·7	0·51	3617	34	140	(3460)	—	(15)					
VI[a]		sat. soln	20·0	3617										

		26·8	1·0	3624	—	(20)	3400	278	210	0·51	1740[c]	18	470	
	$O_3\cdots O_7$–4·2	16·8	1·0	3624	—	(25)	3405	275	205	0·51	1740[c]	18	475	
VII	$O_3\cdots O_{12}$–5·2	12·9	1·0	3624	—	(30)	3416	263	190	0·51	1740	18	475	3455 ± 55
	$O_7\cdots O_{12}$–4·3	5·41	5·0	3626	(44)	45	3414	248	175	1·0	1741	17	475	
		1·095	20·0	3626	32	85	3452	214	115	5·0	1742	18	480	
		0·225	60·0	3627	32	145	(3452)	—	60	20·0	1741	17	480	
VIII		3·0	20·0	3629	22	90	3445	275	45					
		10·59	2·0	3624	31	45	3446	255	145					
IX		5·57	5·0	3626	30	60	3448	248	130					1460 ± 40
		0·557	20·0	3627	27	135	(3448)	(200)	45					
X	6·6	41·4	2·0	3631	26	85	3505[b]	(130)	15	0·11	1742	18	460	
XI	6·6	12·0	2·0	3630	26	105	—	—	—	0·11	1718	18	450	
XII	7·6	3·0	20·0	3619	23	95	(3380)	—	(5)					50 ± 20
				3647	—	45	—	—	—					
XIII	7·0	sat. soln	2·0	3617										

ν and $\Delta\nu_{\frac{1}{2}}$ are in cm^{-1}. Values in parenthesis are approximate; [a] O···O. νOH(free) = 0·18; νOH(bonded) = 0. [b] asym band; [c] shoulder at ~1,719; K = [dimer/(monomer)^2] l./mole. In all compounds studied except compound IX it was used the highest possible concentration in CCl_4. The distance between O···O was determined on the Dreiding molecular models.

TABLE 2. HYDROXYL AND CARBONYL ABSORPTIONS OF HYDROXYSTEROIDS IN $CHCl_3$

Compound No.	Conc (mM)	Cell paths (mm)	νOH						Cell path (mm)	νCO		
			Free			Bonded						
			ν	$\Delta\nu_{\frac{1}{2}a}$	ε_a	ν	$\Delta\nu_{\frac{1}{2}a}$	ε_a		ν	$\Delta\nu_{\frac{1}{2}a}$	ε_a
IV	50	1·0	3619	28	130	(3470)	—	(10)				
V	35·7	0·51	3617	32	140	(3450)	—	(5)				
	103·1	0·51	3619	48	80	3435	216	125	0·11	1731	28	405
	30·4	1·0	3619	43	140	3448	175	35	0·51	1732	27	400
	6·09	2·0	3620	41	175	(3455)	—	(15)	2·0	1733	27	400
	3·045	5·0	3620	40	185	(3455)	—	(10)	2·0	1732	28	400
	1·522	5·0	3620	40	200	—	—	—	5·0	1733	27	400
VIII	50·0	1·0	3613	32	130	3450	—	35				
XII	50·0	1·0	3610	45	115	(3455)	—	10				

ν and $\Delta\nu_{\frac{1}{2}a}$ are in cm^{-1}. Values in parenthesis are approximate.

Compound XII exhibits only a very weak association probably due to the large distance between the OH groups (O · · · O, 7·6 Å, Table 1). Thus, this compound cannot associate in the same way as compounds I, VII and IX.

In bringing about association, an OH group attached to the side chain (II, IV, VI and XIII) is much less effective than one axially substituted on the α-face of the main skeleton. The freedom of movement of the side chain inevitably means that there is less chance of the OH being in the right position for successful H-bonding.

Intramolecular H-bonding in compounds III, IV, V, VI and XIII is impossible for the large distances between the OH group bonded on the C_{24}-atom and the OH group attached on steroidal skeleton (Table 1).

The association of dihydroxy steroids, showing a very weak self-association, in mixtures with some diketo steroids and other dibasic compounds, no marked change in the association was observed.

The abnormally strong H-bonding revealed in the present work may be related to the specific biological action of the bile salts of the amino acid peptide conjugates of

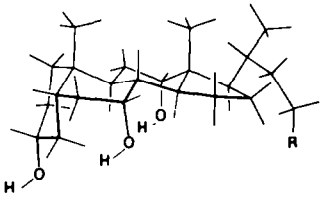


FIG. 1. Planar projection of the Dreiding molecular model of VII. The front edge of the molecule is depicted by heavy lines. The C—O bonds are in a fixed orientation parallel to one another and perpendicular to the plane through rings B, C and D.

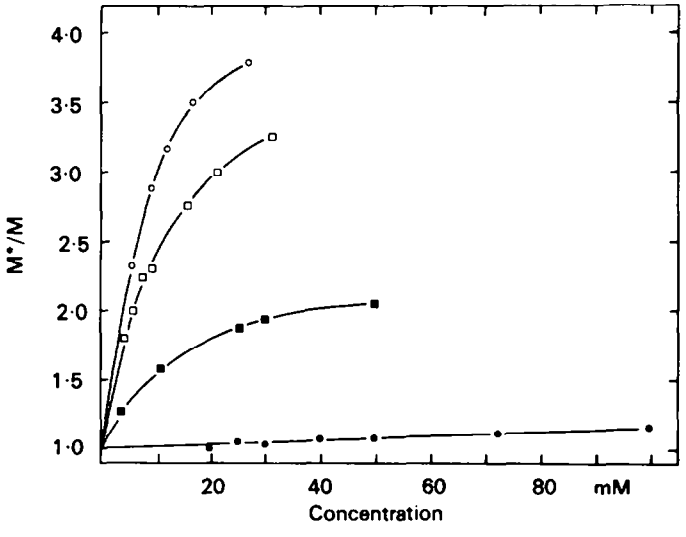


FIG. 2. Plot of the ratio M*/M of the apparent (M*) to true (M) mol wt against molar concentration for solutions in CCl_4: ○—(VII); □—(IX); ■—(I) and ●—3α-hydroxy-3β-methyl-cholestane was included only for comparison (the course of line typical for polymeric association).

hydroxycholanic acids. There is some likelihood that micelle formation involving fats may be partly controlled by the multiple association of hydroxyls.

This type of self-association clearly requires further study, though it is, of course, but one instance of the general problem of the stereochemistry and stoichiometry of intermolecular association.

EXPERIMENTAL

IR spectra were recorded with a Unicam S.P. 100 double beam spectrophotometer equipped with an S.P. 130 NaCl prism-grating double monochromator [3000 lines per inch (2150–3650 cm^{-1}) and 1500 lines per inch (650–2150 cm^{-1})] operated under the general procedure described previously.[13]

The apparent half-bands widths, $\Delta\nu_{\frac{1}{2}}$, are quoted to the nearest integer; where necessary they were determined by reflection of the undisturbed wings of the unsymmetrical bands. Intensities are given as apparent molar absorptivities, ε_a, (l. $mole^{-1}$ cm^{-1}) rounded to the nearest 5 units.

The mol wts of compounds were measured with a Mechrolab vapour pressure osmometer model 301 A precalibrated with benzil in CCl_4.

Association constants, K = (dimer)/(monomer)^2 in l./mole, were calculated from the Mecke–Kempter equation[18] and are very approximate, but serve as a guide to the degree of association.

Materials. Analar CCl_4 was used without further purification. Analar $CHCl_3$ was freed from EtOH and water by two successive passages through a column of blue silica gel immediately before use. All samples were of chromatographical purity and the physical constants agreed well with those in literature. Compounds I and II were kindly supplied by Dr. C. J. W. Brooks; X and XII by Dr. I. M. Campbell, both of Glasgow University and IX by Prof. F. Klyne of Westfield College, London University and other compounds by M. Martin-Smith of Royal School of Pharmacy, Glasgow.

Acknowledgement—We wich to thank the British Council for the award (to S.K.) of a fellowship. We also thank Mrs. F. Lawrie for assistance with some of the measurements and the following colleagues for generously supplying samples: C. J. W. Brooks, I. M. Campbell, M. Martin-Smith and Professor F. Klyne.

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