

## A Method for Distinguishing between Inter- and Intramolecular Hydrogen Bonding

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A method has been investigated for distinguishing between inter- and intramolecular hydrogen bonding in hydroxy-carbonyl compounds with the aid of infra-red measurements. It is based on the fact that compounds containing intermolecular hydrogen bonds exhibit considerably higher carbonyl frequencies in dioxan solution than in the pure state and that compounds capable of intramolecular hydrogen bonding show only small differences. This method has been applied to pannaric acid, giving support for the structure previously proposed. The infra-red results were also confirmed by ultraviolet absorption data.

**D**uring studies on the lichen constituents pannaric acid<sup>1</sup> and calycin<sup>2</sup> it became desirable to determine the type of hydrogen bonding present in these compounds.

It is sometimes difficult to decide if a compound contains intramolecular hydrogen bonds or whether hydrogen bonds are formed between neighbouring molecules.

A common method is to study the stretching frequency of a hydrogen bonded hydroxy or amino group at various concentrations in an inert solvent such as carbon tetrachloride. In a similar way the shift in the nuclear magnetic resonance of a hydrogen bonded proton can be investigated. However, the type of hydrogen bonding in compounds, which are only slightly soluble in carbon tetrachloride, for example pannaric acid and calycin, cannot be determined with these methods. For compounds containing hydrogen bonded carbonyl groups a simple infra-red method has been developed using dioxan as solvent.

Dioxan and similar solvents form complexes with hydroxy groups<sup>3-8</sup>, effectively disrupting even strong intermolecular hydrogen bonds. Compounds containing such bonds should thus exhibit considerably higher carbonyl stretching frequencies in dioxan solution than in the pure state. Strong intramolecular hydrogen bonds, on the other hand, are almost unaffected by dioxan (*cf.* Ref.<sup>9</sup>). Compounds forming intramolecular hydrogen bonds there-

Table 1. Infra-red carbonyl absorption of hydrogen bonded compounds in the pure state and in solution.

Compound		$\nu_{\text{CO}}$ (pure compound)	$\nu_{\text{CO}}$ (solution)	Shift $\text{cm}^{-1}$
<i>o</i> -Hydroxybenzaldehyde	(ch)	1 662 <sup>c</sup>	1 665 <sup>d</sup>	3
<i>p</i> -Hydroxybenzaldehyde	(i)	1 665 <sup>a</sup>	1 688 <sup>d</sup>	23
		1 670 <sup>b</sup>		18
<i>o</i> -Hydroxyacetophenone	(ch)	1 640 <sup>c</sup>	1 640 <sup>d</sup> (1 640 <sup>e</sup> )	0 (0)
<i>p</i> -Hydroxyacetophenone	(i)	1 658 <sup>a</sup>	1 678 <sup>d</sup> (1 672 <sup>e</sup> )	20 (14)
		1 663 <sup>b</sup>		15
Methyl <i>o</i> -hydroxybenzoate	(ch)	1 675 <sup>c</sup>	1 677 <sup>d</sup> (1 675 <sup>e</sup> )	2 (0)
Methyl <i>p</i> -hydroxybenzoate	(i)	1 680 <sup>a</sup>	1 720 <sup>d</sup> (1 710 <sup>e</sup> )	40 (30)
		1 682 <sup>b</sup>		38
2-Hydroxy-1-naphthaldehyde	(ch)	1 635 <sup>a</sup>	1 645 <sup>d</sup>	10
		* 1 637 <sup>b</sup>		8
Acetylacetone	(ch)	** 1 616 <sup>c</sup>	1 617 <sup>d</sup>	1
Dimedone	(i)	‡ 1 618—1 610 <sup>a</sup>	1 655 <sup>d</sup>	41 (av)
		‡ 1 615 <sup>b</sup>		40
Salicylic acid	(ch)	‡‡ 1 665 <sup>a</sup>	1 680 <sup>d</sup> (1 675 <sup>e</sup> )	15 (10)
<i>p</i> -Hydroxybenzoic acid	(i)	‡‡ 1 687 <sup>a</sup>	1 718 <sup>d</sup> (1 707 <sup>e</sup> )	31 (20)
Pannaric acid (I)	(ch)	1 662 <sup>a</sup>	1 658 <sup>e</sup>	-4
	(i)	1 690 <sup>a</sup>	1 710 <sup>e</sup>	20
Dimethyl pannarate (II)	(ch)	1 657 <sup>a</sup>	1 660 <sup>e</sup>	3
	(i)	1 688 <sup>a</sup>	1 715 <sup>e</sup>	27

Infra-red absorption in KBr (a), in nujol (b), as liquid (c), in dioxan (d) and in THF (e). i = intermolecular hydrogen bonding; ch = chelation; av = average; \* Ref.<sup>19</sup> \*\* Ref.<sup>20</sup> ‡ Ref.<sup>21</sup> ‡‡ Ref.<sup>22</sup>

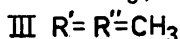
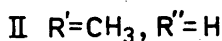
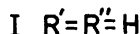
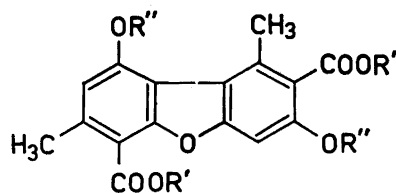
fore show approximately the same carbonyl frequency in dioxan solution and in the pure state. It should thus be possible to establish the type of hydrogen bonding by measuring the carbonyl frequencies of a compound in the pure state and in dioxan solution. To test this, a number of simple compounds capable of either inter- or intramolecular hydrogen bonding were investigated.

The infra-red measurements on pure solid compounds were done in potassium bromide discs or nujol mulls. Different results are sometimes obtained with these two techniques but in our case only small differences were observed (Table 1).

#### INFRA-RED ABSORPTION MEASUREMENTS

The results of the measurements are listed in Table 1. As expected, compounds containing only intermolecular hydrogen bonds showed considerably higher carbonyl frequencies in dioxan solution than in the pure state. The difference varied from 20  $\text{cm}^{-1}$  for *p*-hydroxyacetophenone to 41  $\text{cm}^{-1}$  for dimedone. The intramolecularly hydrogen bonded compounds behaved quite differently, showing comparatively small shifts (0–10  $\text{cm}^{-1}$ ). The only exception was salicylic acid which exhibited a shift of 15  $\text{cm}^{-1}$ . This is probably due to the fact that the carboxyl group in salicylic acid can take part in both inter- and intramolecular hydrogen bonding as indicated by X-ray data<sup>10</sup>. Methyl salicylate behaved normally (Table 1). It might thus be advisable to esterify carboxyl groups prior to measurements.

In some cases, the more polar tetrahydrofuran (THF) was used as solvent in place of dioxan. The difference between the carbonyl frequency of the compound in the pure state and in solution was then decreased. *p*-Hydroxyacetophenone and *p*-hydroxybenzoic acid, for example, showed shifts of 14 and 20  $\text{cm}^{-1}$  respectively. However, inter- and intramolecular hydrogen bonding could still be distinguished since for *o*-hydroxyacetophenone no shift was observed and for salicylic acid a shift of 10  $\text{cm}^{-1}$  only.



Pannaric acid which has been assigned structure (I) was also investigated. THF was used as solvent since both pannaric acid and its dimethyl ester were only slightly soluble in dioxan. In the pure state, pannaric acid and dimethyl pannarate showed two overlapping carbonyl bands. In THF one band was considerably shifted to a higher frequency (Table 1). Pannaric acid must therefore contain one inter- and one intramolecularly hydrogen bonded carbonyl group in agreement with the proposed structure (I).

#### ULTRAVIOLET ABSORPTION MEASUREMENTS

An attempt was also made to correlate infra-red and ultraviolet absorption data.

Table 2. Ultraviolet absorption of hydrogen bonded compounds and their methyl ethers.

Compound		UV absorption in dioxan	UV absorption of O-methyl deri- vative in dioxan	Shift on methylation ( $\text{m}\mu$ )
<i>o</i> -Hydroxybenzaldehyde	(ch)	325	313	-12
<i>p</i> -Hydroxybenzaldehyde	(i)	269	270	+ 1
<i>o</i> -Hydroxyacetophenone	(ch)	322	301	-21
<i>p</i> -Hydroxyacetophenone	(i)	265	266	+ 1
Methyl <i>o</i> -hydroxybenzoate	(ch)	306	292	-14
Methyl <i>p</i> -hydroxybenzoate	(i)	252	253, 255	+ 2 (av)
Methyl 3-hydroxy-2-naphtoate	(ch)	* 366	* 338	-28
Acetylacetone	(ch)	273	251	-22
Dimedone	(i)	** 244	243	- 1
Dimethyl pannarate	(ch)	335 (sh)	299	-36
	(i)	302 (sh)	299	- 3

i, ch, av, see Table 1. sh = shoulder. \* Ref.<sup>23</sup> \*\* Ref.<sup>21</sup>

The type of hydrogen bonding in a phenolic compound can often be determined by measuring the difference in wavelength between corresponding ultraviolet absorption peaks in the compound and its O-methyl derivative. A red-shift on methylation indicates intermolecular hydrogen bonding, whereas a blue-shift is observed for compounds which form intramolecular hydrogen bonds<sup>11-13</sup>. These measurements have generally been made in non-polar solvents which are often unsuitable for hydroxyl compounds (*cf.* however Refs. 13,23). Dimedone, for example, has been shown to exist almost exclusively in the diketo form in carbon tetrachloride<sup>14</sup>. In our measurements dioxan was therefore used as solvent.

The results of the measurements are shown in Table 2. The closest correlation between the type of hydrogen bonding and the wavelength shift on methylation was found for the strong absorption ( $\epsilon > 10^3$ ) which appeared at 250–325  $m\mu$  in the simple phenolic compounds investigated. Only these shifts are therefore listed.

Both hydrogen bonding with dioxan and methylation of a hydroxyl group which is part of a chromophoric system, seem to have similar effects on the ultraviolet absorption of this system. Thus in dioxan solution compounds containing intermolecular hydrogen bonding showed absorption maxima at approximately the same wavelength as the corresponding methyl ethers. Since strong intramolecular hydrogen bonds, on the other hand, are unaffected by dioxan, the chelates investigated exhibited large blue-shifts on methylation ( $\geq 14 m\mu$ ).

The measurements were also extended to dimethyl pannarate (Table 2) but the conclusions are somewhat uncertain owing to the complexity of the absorption spectrum in the relevant region.

Although the interpretation may be difficult, ultraviolet absorption data can undoubtedly often be used to support the results from infra-red measurements.

Table 3. Infra-red carbonyl absorption of non hydrogen bonded compounds in the pure state and in solution.

Compound	$\nu_{\text{CO}}$ (pure)	$\nu_{\text{CO}}$ (dioxan solution)	Shift $\text{cm}^{-1}$
<i>o</i> -Methoxybenzaldehyde	1 685 <sup>c</sup>	1 690	5
<i>p</i> -Methoxybenzaldehyde	1 685 <sup>c</sup>	1 675	–10
<i>o</i> -Methoxyacetophenone	1 675 <sup>c</sup>	1 665	–10
<i>p</i> -Methoxyacetophenone	1 677 <sup>a</sup>	1 682	5
Methyl <i>o</i> -methoxybenzoate	1 720 <sup>c</sup>	1 730	10
Methyl <i>p</i> -methoxybenzoate	1 710 <sup>a</sup>	1 717	7
Benzophenone	1 655 <sup>a</sup>	1 662	7
Anthraquinone	1 677 <sup>a</sup>	1 677	0
Fluorenone	1 710 <sup>a</sup>	1 720	10
Permethyl pannarate (III)	1 722 <sup>a</sup>	1 727	5

a, c, i, ch, see Table 1.

## CONCLUSIONS

The close dependence of the hydroxyl stretching frequency on both the O—H distance of the hydrogen bonded group and on the O—O distance of the O—H...O bond has been demonstrated<sup>15</sup>. In both solid and liquid compounds the shift in hydroxyl frequency on hydrogen bonding and the strength of the bond are also closely related<sup>16</sup>. Although the changes in carbonyl frequency are generally smaller, they show the same trend as the shifts in hydroxyl frequency<sup>17</sup>. It therefore seems probable that other intermolecular effects are negligible in comparison with strong hydrogen bonding. For some carbonyl compounds containing no hydroxyl groups, the difference in carbonyl frequency in the pure state and in solution was generally small (Table 3; cf. also Ref.<sup>18</sup>).

The comparison between the carbonyl frequencies of a hydroxy-carbonyl compound in pure liquid or solid state and in dioxan solution thus offers a simple method for distinguishing between strong inter- and intramolecular hydrogen bonds. It seems likely that a similar method can be applied also to other hydrogen bonded systems.

## EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage. Infra-red measurements were done on a Perkin-Elmer spectrophotometer Nr 21, fitted with a sodium chloride prism. The absorption of the solvent was compensated. Solids were investigated in potassium bromide discs or in nujol mull and oils as liquid films. The concentration of the solutions measured varied between 0.2 and 0.05 M depending on the solubility. Spectra were taken in a 0.1 mm cell.

Ultraviolet absorption spectra were recorded with a Beckman DK-2 spectrophotometer.

Dioxan was purified according to Hess *et al.*<sup>24</sup> THF was refluxed 96 h with sodium wire prior to distillation. No carbonyl absorption was detected in the pure solvents.

The materials used were generally commercial samples, purified to the literature constants.

*o*-Methoxyacetophenone (b.p.<sub>20</sub> 131–132°) and methyl *o*-methoxybenzoate (b.p.<sub>12</sub> 127°) were prepared from *o*-hydroxyacetophenone and methyl salicylate, respectively, by methylation (dimethyl sulfate and potassium carbonate in acetone).

*Acknowledgements.* The author would like to thank Professor H. Erdtman for his encouragement and kind interest in this work. Thanks are also due to Miss G. Hammarberg and Mr. E. Pettersson for infra-red and ultraviolet absorption measurements and to Dr. I. Wellings for checking the English.

Financial support from *Statens Tekniska Forskningsråd* is gratefully acknowledged.

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Received January 10, 1961.