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SPECTROSCOPIC STUDIES OF KETO-ENOL EQUILIBRIA-X

MULTIPLE HYDROGEN BONDS[1]

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Abstract—The tautomeric systems, *o*-(acetoacetyl)phenol, 2-(acetoacetyl)-1-naphthol, 2-(acetoacetyl)-4-methylphenol, salicyloylacetaldehyde and Schiff bases derived therefrom, using both normal and N^{15} labeled amines, have been investigated by PMR and IR spectroscopy. The ability of one acceptor group to simultaneously associate with two protons in strong hydrogen bonds is discussed.

INTRODUCTION

EXAMPLES of two protons simultaneously associated with one acceptor group such as C=O or C=N have appeared in the chemical literature.[2-5] However to the best of our knowledge, only a limited discussion of the strength of such "double" hydrogen bonds is available.[5] In this paper, we wish to present evidence that the strength of "double" hydrogen bonds is similar to that of more normal single hydrogen bonds.

This bonding is of particular interest in that aureomycin, a tetracycline antibiotic, possesses comparable multiple hydrogen bonds. Donahue *et al.*[2] have carried out careful crystallographic analysis of this molecule and their results indicate the hydrogen bonds in crystalline aureomycin are strong.

A group of Schiff bases obtained by condensing salicylaldehydes and *o*-aminophenols were briefly investigated.[3] However these compounds are extremely insoluble in any solvents useful for hydrogen bonding studies by PMR spectroscopy (such as $CDCl_3$). In addition, one chelate system requires a 5-membered ring which sterically is not as favorable as a 6-membered ring.

Merrill[4] studied various 2,2-dihydroxybenzophenones and found that both phenolic hydrogens were strongly associated to the C=O group. The hydrogen bond in the dihydroxy compound was found to be weaker than the one in hydroxybenzophenone. This was attributed to the steric interactions between the two 5-hydrogens which twists each phenyl from the plane of the C=O group by an estimated 15°. The resulting non-planarity weakens any resonance interactions in the system. In the mono-hydroxy compound, the unsubstituted ring could twist leaving an unstrained chelate system.

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[1] Part IX: G. Dudek and E. P. Dudek, *J. Am. Chem. Soc.* **88**, 2407 (1966).

[2] J. Donahue, J. Dunitz, K. N. Trueblood, and M. S. Webster, *J. Am. Chem. Soc.* **85**, 851 (1963).

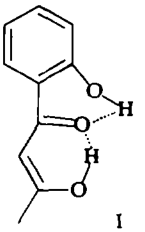
[3] A. W. Baker and A. T. Shulgin, *J. Am. Chem. Soc.* **81**, 1523 (1959).

[4] J. R. Merrill, *J. Phys. Chem.* **65**, 2023 (1961).

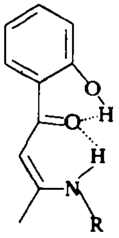
[5] G. C. Pimentel and A. L. McCellan, *The Hydrogen Bond*. Freeman, San Francisco (1960); *Hydrogen Bonding* (Edited by D. Hadzi). Pergamon Press, New York (1959).

Compounds such as *o*-(acetoacetyl)phenol (I) and 2-(acetoacetyl)-1-naphthol (IIIA) are ideal systems for studying the effect of multiple hydrogen bonds.[6] Both hydrogen bonds are strong in the enol tautomer of the parent molecule, and, according to molecular models, steric interactions are minimal.[7] The entire system can be planar.

The aceto carbonyl is readily attacked by amines to form Schiff bases (II).[6, 8] The product provides a situation where the two groups bonded to the C=O are not alike—a hydroxyl and an amine versus two hydroxyls in the parent molecule.



I



II

In Table 1, some of the properties of the oxygen systems (I and III) and of several reference compounds are listed. The PMR data indicate that the hydrogen bonds in *o*-(acetoacetyl) phenol (I) and 2-(acetoacetyl)-1-naphthol (III) are strong and

Table 1. PMR data for the acetoacetyl-phenols and naphthols

Compound		Solv	Temp	Hydroxyl PMR Shifts[a]	
o-(Acetoacetyl)phenol (I)		CCl_4	30°	11·80	14·84
	0·35M	$CDCl_3$	30°	12·07	14·96
	0·6M	$CDCl_3$	30°	12·07	15·03
			0°	12·19	14·97
2-(Acetoacetyl)-1-naphthol (IIIA)	0·25M	CCl_4	30°	13·54	14·82
	0·8M	$CDCl_3$	30°	13·65	14·91
	0·4M	$CDCl_3$	30°	13·65	14·95
	0·2M	$CDCl_3$	30°	13·68	14·97
2-(Acetoacetyl)-4-methyl-phenol		$CDCl_3$	29°	11·90	15·01
o-Hydroxyacetophenone[b]		CCl_4		12·07	
Salicylaldehyde[b]		CCl_4		10·91	
1-Hydroxy-2-acetonaphthone[b]		CCl_4 $CDCl_3$		13·92 13·98	
Phenyl-1,3-butane-dione[b]		CCl_4			16·2
2,4-Pentane-dione[b]		CCl_4			15·3
p-Hydroxyacetophenone[b]		$CDCl_3$		~5	

[a] In ppm from TMS. [b] Data from Ref. 9.

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[6] G. Wittig, *Ber. Dtsch. Chem. Ges.* **60**, 1085 (1927).

[7] Stuart-Briegleb Models manufactured by E. Leybold's Nachfolger, Germany, were utilized.

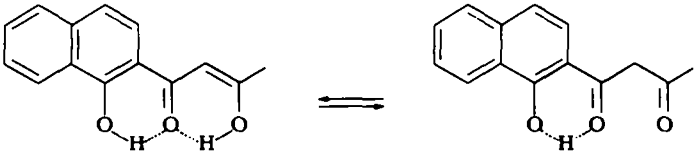
[8] W. Baker, J. B. Harborne and W. D. Ollis, *J. Chem. Soc.* 3215 (1952).

[9] G. Dudek, *J. Org. Chem.* **30**, 548 (1965).

concentration independent. The chemical shift of the enol proton is essentially unaltered when the aromatic portion of the molecule is changed from benzene (I) to naphthalene (III). However, the "phenolic" OH shifts downfield by 1·5 ppm upon the addition of the second aromatic ring. On this basis, the PMR band positions were assigned. Although we have drawn only one resonance structure for I and III, others are implied, especially by the large PMR shifts.[9]

The hydroxyl IR stretching band of I consists of a broad signal ($\sim 400\ \mathrm{cm}^{-1}$ wide) centered at about $3050\ \mathrm{cm}^{-1}$. The band could result from two broad, overlapping OH absorptions. Both the position of the band(s) and the extreme width are compatible with strong intramolecular association.[9]

The enol tautomer is the major form of both *o*-(acetoacetyl) phenol and 2-(acetoacetyl)-1-naphthol in carbon tetrachloride solution. On the other hand, in chloroform solutions, small amounts of other species are observed. In the case of the naphthol derivative, the PMR spectrum of a freshly prepared chloroform solutions shows only the presence of the enol form, but upon standing several hours, extraneous material appeared (Fig. 1), which after several days amounted to about 25%. The sluggishness of this process is interesting.



IIIA IIIB

Although other possibilities could be considered, two major species (III A and B) are probably involved in this slowly attained "equilibrium". The prominent PMR resonances occurring at $\delta = 2{\cdot}12$, 6·16, 13·65 and 14·95 ppm are readily assigned to the enol, IIIA. The 2·29 ppm, 4·09 ppm and the weak signal adjacent to the 13·65 ppm band could be assigned to the keto methyl, methylene and phenolic hydrogen of tautomer IIIB[10] respectively (*vide infra*). The integrated peak areas are in agreement with these assignments. The other two small bands in the spectrum of III (Fig. 1) may result from a hemiacetal,[11,12] or from rotational isomers of B, or from decomposition products.

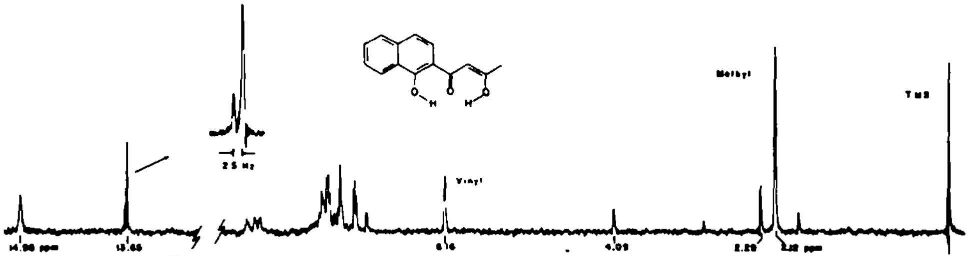


FIG. 1 The PMR spectrum of 2-(acetoacetyl)-1-naphthol ($CDCl_3$ soln).

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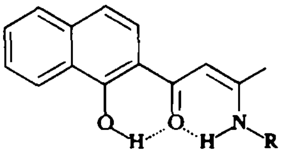
[10] Cf. the spectrum of acetylacetone. L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, p. 70. Pergamon Press, Oxford (1959).

[11] A. F. McDonagh and H. E. Smith, *Chem. Comm.* 374 (1966).

[12] M. V. Bhatt and K. M. Kamath, *Tetrahedron Letters* 3885 (1966) and Refs contained therein.

The IR spectrum of a freshly prepared solution of III shows only the presence of a chelated C=O at 1611 cm^{-1}. After the solution stands a day, two weak bands appear in the spectrum at 1720 and 1680 cm^{-1}, which could arise from the free and chelated carbonyls of B respectively.[9]

The spectra of a freshly prepared solution of 2-(acetoacetyl)-4-methylphenol are consistant with the keto form (similar to IIIB). The PMR spectrum indicates the presence of only one OH resonance and no vinyl resonance. The high field resonances do not rapidly exchange with D_2O, but the OH does exchange. The IR spectrum possesses two bands 1689 and 1721 cm^{-1} which decrease markedly in intensity with time. After equilibrium is established, the PMR and IR spectra of 2-(acetoacetyl)-4-methyl phenol are similar to those of III.



IV

In agreement with previous workers[6,7] the PMR data (Table 2) indicate that the molecule, *o*-(β-methylaminocrotono) phenol (II; R = CH_3) is correctly described as a β-ketoamine. The occurrence of a 5·2 Hz. and a 6·4 Hz. NH—CH spin coupling in the N-methyl and N-benzyl compounds respectively requires that the proton is

Table 2. PMR data for chloroform solutions of the Schiff bases

Compound	NH		OH[a]
	δ[a]	J[b]	
o-Hydroxy-(β-methylamino)crotonophenone	10·8[c]	5·2	13·08[c]
	10·8	5·4	13·60
o-Hydroxy-(β-benzylamino)crotonophenone	11·2	6·4	13·50
o-Hydroxy-(β-hexylamino)crotonophenone	11·0		13·62
o-Hydroxy-(β-[1-phenylethylamino])crotonophenone	11·36	7·8[g]	13·58
	11·29[c]	7·8	13·13[c]
1-Hydroxy-2-(β-benzylamino)crotononaphthone	11·25	6·1	15·20
1-Hydroxy-2-(β-phenylamino)crotononaphthone[d]	12·56		15·00
2-Hydroxy-4-methyl-(β-benzylamino)crotonophenone	11·3	6·3	13·28
o-Hydroxy-(β-methylamino)acrylophenone[d]	9·81	5·1	13·25
β-(Methylamino)crotonophenone[d,e]	11·31	5·3	
β-(Phenylamino)crotonophenone[d,e]	13·11		
3-(Methylamino)acrylophenone[f]	10·2	5·0	
4-(Methylamino)-3-butene-2-one[f]	9·6	5·1	

[a] In ppm from TMS.

[b] In Hertz.

[c] CCl_4 soln.

[d] N^{15} substituted.

[e] Data from Ref. 1.

[f] Data from Ref. 13.

[g] Determined from the splitting of the NH signal, J accurate to ±0·15 Hz.

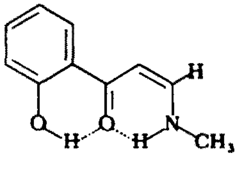
on nitrogen with negligible exchange to oxygen. To confirm the assignment of resonances and structure in the aniline derivative IV (R = Ph), isotopically labeled nitrogen (N^{15}) was employed.[1] The coupling constants not given in Table 2 are listed in Table 3.

TABLE 3. SPIN COUPLING CONSTANTS FOR THE N^{15} SUBSTITUTED COMPOUNDS

Compound	Coupling	J (Hz.)
IV, R = Ph	N^{15}—H	89·5
	N^{15}—CH_3	2·0[a]
	N^{15}—vinyl	4·1
V	N^{15}—H	92·5
	N^{15}—CH_3	1·5[b]
	N^{15}—vinyl	4·2
	NH—ald.	13·1
	HC=CH	7·6

[a] aceto methyl. [b] N-methyl.

Since a large number of spin coupling constants could be obtained from *o*-hydroxy (β-methylamino) acrylophenone (V), the N^{15} substituted analog was likewise synthesized (Fig. 2). The recorded coupling constants are listed in Table 3. The "aldehydic"



V

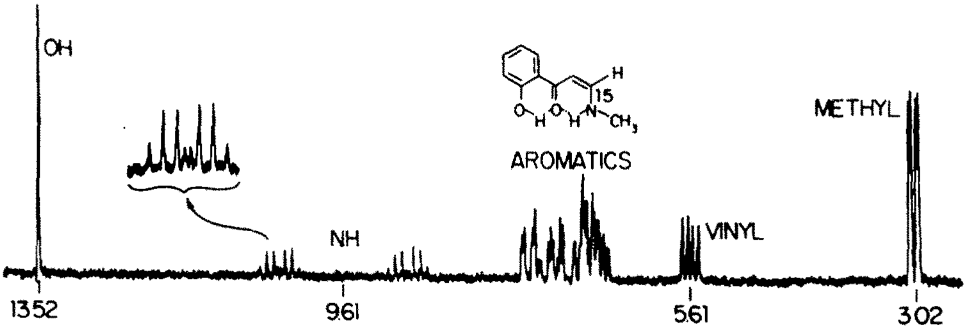


FIG. 2 The PMR spectrum of *o*-hydroxy (β-methylamino) acrylophenone-N^{15} ($CDCl_3$ soln).

proton was not observed in the PMR spectrum as it is buried in the complex ABCD system due to the aromatic protons. The integrated peak areas support this conclusion. The proton–proton spin couplings measured for this compound are comparable to those previously obtained for similar β-amino-aldehydes.[13]