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NMR Spectroscopic Studies of the Tautomerism in Tetramic Acid Analogs and Their Anilides. III.[1] Polar Solvent Effects on the Tautomeric Populations*

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Synopsis. NMR spectroscopic studies of 3-acetyltetramic acid† (3-acetyl-2,4-azolidinedione), 3-acetyltetronic acid† (3-acetyl-2,4-oxolanedione), 3-acetylthiotetronic acid† (3-acetyl-2,4-thiolanedione) and their anilides† (3-(2-phenyliminoethyl) derivatives) showed variations in the tautomeric equilibria with certain polar solvents. For example, the strong solvation effect of DMSO-d_6 causes a predominance of the lactim forms of 3-acetyltetramic acid over the lactam forms and up-field shifts of the enolic protons.

Previously, the tautomeric equilibria of 3-acetyltetramic acid analogs (I—III)† and their anilides (IA—IIIA)† in chloroform-*d* were studied by means of NMR spectroscopy.[1,2] In chloroform-*d*, the spectra of I—III showed the splitting of methylene proton signals by "external" (*cis-trans*) tautomerization (a, b ⇌ c, d), besides the splitting of methyl proton signals by the "internal" prototropy (a⇌b, c⇌d), caused by the different anisotropic effect of the carbonyl group in each tautomer (Chart 1, a—d).[1]

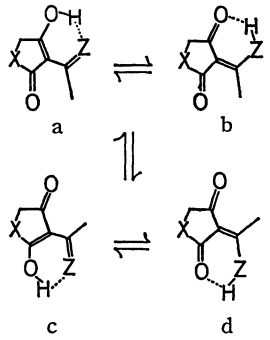

Chart 1.

However, with some exceptions, the splittings in methyl and methylene signals could not be observed in any solvents other than chloroform-*d* (Table 1). For this disappearance of the splittings, two reasons can be considered. The one is the rapid tautomeric interconversion accelerated by the polar solvent over the NMR time-scale. The other is the inclination of the tautomeric equilibria to one side as a result of the solvation effect. When DMSO-d_6 was added to the solution of 3-acetyltetramic acid (I) in chloroform-*d*, the intensity of the methylene signal of the c, d form was successively decreased and extinguished at a DMSO-d_6 content of *ca.* 25%, whereas that of the a, b form was increased. Figure 1a shows the variations in the intensity ratio (c+d)/(a+b) with the DMSO-d_6 content. From this fact, it can be concluded that the acceleration of the prototropy by the polar solvent does not happen in this case.

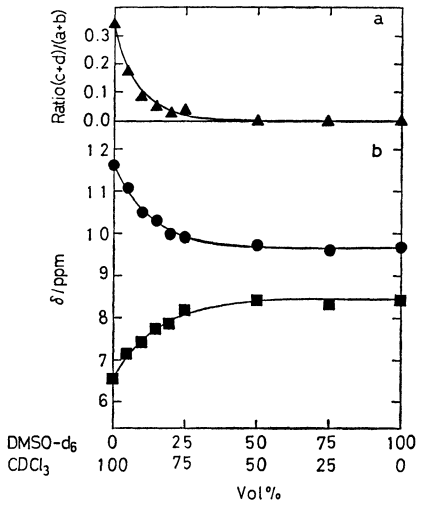

Fig. 1. Variations of the chemical shifts and the tautomeric ratio of 3-acetyltetramic acid (I) in $CDCl_3$-DMSO-d_6 mixed solvent system.
▲: Ratio of c, d form to a, b form, ●: enolic proton, ■: lactam-lactim proton.

Furthermore, along with the addition of DMSO-d_6, the down-field shift of the NH proton signal and the up-field shift of the enolic proton signal were observed throughout this experiment (Fig. 1b). The down-field shift of the NH proton signal suggests the formation of the lactim form, which is then rapidly interconverted with the corresponding lactam form. With the addition of DMSO-d_6, the lactim form should become predominant over the lactam form, since DMSO-d_6 might solvate and stabilize the more polar lactim form.[3]

The up-field shift of the enolic proton is probably caused by the formation of an intermolecular hydrogen

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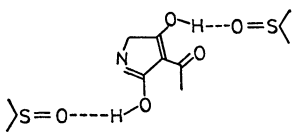
† Common names are consciously introduced for these compounds in order to express the mixed systems of the complicated tautomers. However, the IUPAC names of their keto forms are as follows: 3-acetyl-2,4-azolidinedione (I), 3-acetyl-2,4-oxolanedione (II), 3-acetyl-2,4-thiolandione (III), 3-(2-phenyliminoethyl)-2,4-azolidinedione (IA), 3-(2-phenyliminoethyl)-2,4-oxolanedione (IIA), and 3-(2-phenyliminoethyl)-2,4-thiolanedione (IIIA).

Table 1. NMR chemical shifts and tautomeric populations in various solvents at 34 °C

No.	Compound X	Compound Z	Solvent	Chemical shifts (δ ppm, 100 MHz) CH_3	CH_2	ZH	Tautomeric populations (%) a,b[a]	c,d[a]
I	NH	O	$CDCl_3$	2.49 2.46	3.84 3.97	11.42	77[b]	23
			CD_3CO_2D	2.48	3.75 3.96	c)	24[b]	76
			CF_3CO_2D	2.58	4.18	c)	0	100
			CD_3OD	2.72	4.08	c)	0	100
			DMSO-d_6	2.31	3.70	10.11	100[b]	0
II	O	O	$CDCl_3$	2.55 2.56	4.46 4.68	11.38	36	64
			CD_3CO_2D	2.50	4.60	c)	100	0
			CF_3CO_2D	2.64	4.82	c)	100	0
			CD_3OD	2.80	4.96	c)	100	0
			DMSO-d_6	2.63	4.92	8.20	0	100
			C_5D_5N	2.78	4.53	14.72	0	100
III	S	O	$CDCl_3$	2.54 2.56	3.83 4.04	14.96	24	76
			CCl_4	2.84	3.97 4.20	15.83	17	83
			CD_3CO_2D	2.52	4.05	c)	100	0
			CF_3CO_2D	2.69	4.13	c)	100	0
			CD_3OD	2.80	4.30	c)	100	0
			DMSO-d_6	2.63	4.93	9.62	0	100
IA	NH	NPh	$CDCl_3$	2.53 2.57	3.76 3.82	12.09 12.03	53[b]	47
			CD_3CO_2D	2.52	3.78 3.86	c) c)	32[b]	68
			CF_3CO_2D	2.85	4.18	c) c)	0	100
			CD_3OD	2.78	4.02 4.08	c) c)	64[b]	36
			DMSO-d_6	2.17 2.20	3.56 3.64	12.22 12.31	72[b]	28
IIA	O	NPh	$CDCl_3$	2.54 2.58	4.48 4.53	11.66 12.44	26	74
			CD_3CO_2D	2.50	4.60	c) c)	100	0
			CF_3CO_2D	2.64	4.82	c) c)	100	0
			DMSO-d_6	2.48	4.51	12.01	0	100
IIIA	S	NPh	$CDCl_3$	2.73	4.04 4.13	13.83 14.09	22	78
			CD_3OD	2.78	4.08	c) c)	100	0
			CF_3CO_2D	2.66	4.12	c) c)	100	0
			DMSO-d_6	2.78	4.22	c) c)	0	100

a) For IA-IIIA, the a and c forms were not detected. b) For I and IA, the corresponding lactim forms are included in the populations of the a and b form. c) Extinguished by the rapid H-D exchange reactions with the deuterated solvents.



I-b lactim form

Chart 2.

bonding between I and the DMSO-d_6 molecule. Similar shifts could be observed with respect to II and III. However, further investigations might be necessary with regard to this problem.

In a similar way, major tautomers of the other analogs in various solvents were determined by the measurement of the variations in the methylene signal intensities in mixed solvent systems with chloroform-*d*.

Experimental

The compounds (I—IIIA) were prepared by the methods of the literature cited in the preceding papers.[1,2] All the deuterated solvents were obtained from E. Merck, Ltd. Solutions for the measurements were made so as to contain 1.5×10^{-4} mol of the compounds in 0.4 ml of the solvents. The NMR spectra were recorded on a JEOL PS-100 spectrometer at 100 MHz at 34 °C, using TMS as the internal standard.

References

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