Nuclear Magnetic Resonance Spectroscopic Studies on the Tautomerism in Tetramic Acid Analogues and Their Anilides. Part 4.[1] Interpretation of Carbon-13 Spectra by Molecular Orbital Calculations

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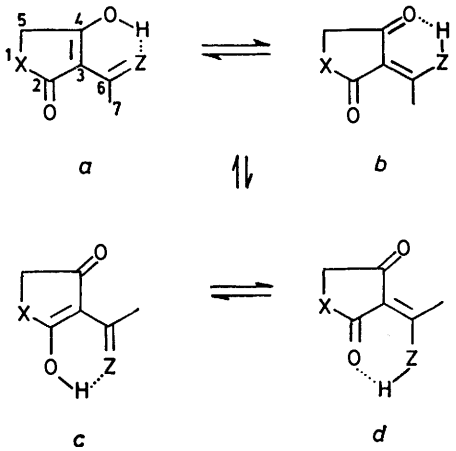
The tautomeric structures of 3-acetyltetramic acid (I), 3-acetyltetronic acid (II), and 3-acetylthiotetronic acid (III), and their anilides (Ia)—(IIIa) in $CDCl_3$ have been studied by Fourier-transform ^{13}C spectroscopy. On the basis of electronic theory, ^1H-partial and gated decoupling techniques allowed the assignment of all signals in the spectra. Unusual features of the spectra were the large up-field shifts of the olefinic carbon signals, and the appearance of signals for the thiol-lactone carbonyl carbons of (III) and (IIIa) at lower field than those for the amide and lactone carbonyl carbons. These features are explained in terms of the electron densities on the carbons calculated by CNDO/2 or INDO methods.

TETRAMIC ACID † analogues (I)—(III), having five-membered unsymmetrical ββ′-tricarbonyl structures, are shown to be completely enolized both in the solid state and in solution.[2] These compounds gave different 'internal' tautomers ($a \rightleftharpoons b$, $c \rightleftharpoons d$) as a result of prototropy between the two oxygen atoms, besides 'external' (*cis–trans*) tautomers ($a,b \rightleftharpoons c,d$) from rotation of the side-chain acetyl group.[3] The 'internal' tautomerization was not observed by ^1H spectroscopy



(I; X = NH, Z = O), (II; X = O, Z = O), (III; X = S, Z = O), (Ia; X = NH, Z = NPh), (IIa; X = O, Z = NPh), (IIIa; X = S, Z = NPh).

since these prototropic interconversions were rapid on the n.m.r. time-scale. In contrast, the *cis–trans* isomerisation process could be detected by ^1H spectroscopy by observing the methylene signals. In a previous paper,[4] we reported the tautomeric populations of these compounds in $CDCl_3$. In addition, the predominance of the ketamine form (*b*,*d*) in the anilides (Ia)—(IIIa) has been previously demonstrated on the basis of the ^1H spectroscopic results of the ^{15}N-enriched compounds.[5] Unique features in the tautomeric population of 3-acetylthiotetronic acid (III) and its anilides (IIIa) have also been presented in these papers.

† Common names are consciously introduced for these compounds in order to express the mixed systems of complicated tautomers.

^{13}C N.m.r. techniques are well known to be valuable for studying rapid chemical equilibria[6-8] and, for instance, it is possible to observe the behaviour of carbon atoms involved in tautomerization. This prompted us to examine the ^{13}C spectra of the tetramic acid analogues (I)—(III) and their anilides (Ia)—(IIIa).

EXPERIMENTAL

Compounds (I),[9] (II),[10] (III),[11] and their anilides (Ia)—(IIIa) [12] were prepared according to the procedures described in the literature.

^1H Spectra were recorded on a JEOL PS-100 and/or Hitachi Perkin-Elmer R22 spectrometer at 90 MHz at 303 K.

^{13}C and ^1H FT spectra were recorded on a JNM-FX100 spectrometer equipped with a PFT-100FT accessory at 25.1 MHz and 303 K, using $SiMe_4$ as the internal standard. The samples were run in a solution containing 0.1 g of the compound per cm^3 of $CDCl_3$. A broad-band proton decoupler and/or a gated decoupler were used in assigning carbonyl carbon signals.

CNDO/2 and INDO calculations were performed with the computer programme CNINDO.[13] Bond angles, bond lengths, and geometries of these compounds have been reported previously.[14] The major parts of the calculations were made on the HITAC 8800/8700 computer at the Computer Centre, University of Tokyo.

RESULTS

^{13}C *Spectra.*—^{13}C Chemical shifts and ^{13}C–^1H coupling constants of the carbons C(2)—C(7) in these compounds (I)—(III), (Ia)—(IIIa) are listed in Table 1. Each signal was split into two components by the 'external' tautomerization ($a,b \rightleftharpoons c,d$). Upon lowering the sample temperature to 203 K, no signal for the 'internal' tautomerization ($a \rightleftharpoons b,c \rightleftharpoons d$) was observed in the ^{13}C spectra.

The methyl (C-7), methylene (C-5), and olefinic (C-3) carbons could be easily assigned to the corresponding signals by means of the ^1H-partial decoupled (off-resonance) measurement. Here, it is noteworthy that the C-3 signals of these compounds appeared 90—110 p.p.m. to higher field compared with those of ordinary olefinic carbons.

With respect to the carbonyl carbons (C-2,4,6) in compounds (I)—(III), it was necessary to assign the signals with care. Thus it is known from consideration of inductive and mesomeric effects that signals of the hydrogen-bonded carbonyl carbons shift to lower field compared with those

TABLE 1

^{13}C Chemical shifts (δ/p.p.m. from $SiMe_4$) and ^{13}C–^1H coupling constants (Hz, parentheses) of tetramic acid analogues and their anilides in $CDCl_3$ at 25.1 MHz and 303 K

Compounds		Carbons					
No.	Tautomeric forms	C-2 (^3J)	C-4 (^2J)	C-6 (^2J)	C-3	C-5	C-7
(I)	*a,b*	176.0 (3.3)	193.1 (5.6)	185.3 (6.3)	101.8	51.8	19.7
	c,d	169.8 (*)	199.3 (*)	189.5 (*)	101.8	48.6	20.6
(II)	*a,b*	176.4 (3.3)	192.3 (5.1)	188.1 (6.1)	97.8	73.7	19.7
	c,d	168.2 (2.0)	197.7 (4.4)	194.0 (5.6)	100.1	68.9	22.2
(III)	*a,b*	202.8 (3.0)	193.2 (5.8)	188.9 (6.3)	107.5	39.3	20.0
	c,d	191.5 (2.8)	198.8 (6.2)	196.0 (6.3)	110.5	35.3	24.1
(Ia)	*b*	173.4 (3.0)	197.3 (4.2)	167.0 (†)	98.4	51.0	16.0
	d	176.1 (2.8)	194.3 (4.5)	166.6 (†)	96.5	49.6	15.2
(IIa)	*b*	175.8 (2.8)	193.7 (4.2)	169.1 (†)	91.6	72.2	16.1
	d	171.8 (2.7)	197.2 (4.3)	170.1 (†)	93.0	70.1	15.7
(IIIa)	*b*	199.1 (*)	195.2 (5.9)	169.1 (†)	102.5	38.4	16.3
	d	193.9 (2.1)	198.9 (5.6)	169.3 (†)	103.1	37.3	16.4

* Not detected by the overlap. † Multiple couplings with aromatic protons.

for free carbonyl carbons, whereas the enolized ones shift to higher field.[8a,c] However, the carbonyl region of these compounds is quite complex (Figure), since each chemical shift might correspond to a weighted average for each pair of the 'internal' tautomeric forms, *i.e.* *a* and *b,c*, and *d*. The measurement of long-range ^{13}C–^1H coupling (gated-decoupling) offered a resolution to this problem (Table 1). For the tetramic acid analogues, double doublet resonances (^2J = 5.6—6.3 Hz) were observed for one pair of signals, which can be ascribed to the acetyl carbonyl carbon (C-6). The other signals were split into triplets. The larger long-range coupling (^3J = 1.9—3.0 Hz) observed for one pair of them probably arises from coupling of C(2) with the methylene proton *via* the heteroatom. The assignment of each component to the *a,b* or *c,d* forms was made on the basis of the above-mentioned electronic theory, the calculated electron densities, and of the ^1H n.m.r. results.

^1H *Spectra.*—Since the 'internal' tautomerization was not detectable by ^{13}C spectroscopy, the ^1H n.m.r. spectra of the tetramic acid analogues (I)—(III) were carefully recorded for the same solutions (at the same temperature) as those used for the ^{13}C spectroscopy. Although splitting of the methylene signals arising from the 'external' interconversion was observed, no splitting was observed for the methyl signal with a CW recording; our earlier results on the 'internal' tautomerization [4] must therefore be retracted. Splitting of the methyl signal was, however, observed for an FT ^1H n.m.r. recording at 223 K.

TABLE 2

Calculated total energy (E_{tot}) and dipole moment (D.M.) by means of CNDO/2 method

Compounds				
No.	Tautomeric forms	$-E_{tot}$ / 10^3 kJ/mol	D.M. / 10^{-29} C m	Population [4,5] (%)
(I)	*a*	301.594	9.87	77
	b	301.596	6.04	
	c	301.574	9.91	23
	d	301.576	6.24	
(II)	*a*	317.202	5.79	36
	b	317.202	13.31	
	c	317.213	2.57	64
	d	317.205	6.97	
(III)	*a*	297.448	6.20	24
	b	297.432	9.44	
	c	297.450	4.80	76
	d	297.415	8.84	
(Ia)	*a*	405.154	6.87	0
	b	405.328	10.04	53
	c	405.149	6.94	0
	d	405.323	11.94	47
(IIa)	*a*	422.380	9.74	0
	b	422.437	10.01	26
	c	422.378	2.97	0
	d	422.522	9.94	74
(IIIa)	*a*	401.487	8.37	0
	b	401.646	10.81	23
	c	401.555	8.07	5
	d	401.663	9.31	72

MO Calculations.—Some investigators have discussed the relative stabilities of tautomeric forms on the basis of molecular orbital calculations.[15a-d] For example, Simon *et al.*[15a] carried out calculations on the various tautomers theoretically possible for 5-nitrobarbituric acid, and showed that the stability difference between the most stable and the least stable species was *ca.* 13 kJ mol^{-1}.

Table 2 lists the total energies (E_{tot}) and dipole moments (D.M.) of (I)—(III) and (Ia)—(IIIa), calculated by the CNDO/2 method. Differences of E_{tot} among the 'external' tautomers (*a,b* ⇌ *c,d*) were *ca.* 17 kJ mol^{-1} for (I), 9 kJ mol^{-1} for (II), and 14 kJ mol^{-1} for (III). The calculated total energies of the tautomeric forms showed a good correlation with the tautomeric populations obtained from the ^1H spectral investigation.[4]

On the other hand, differences of the average E_{tot} of the ketamine form (*b,d*) compared with the enolimine form (*a,c*) were calculated as *ca.* 169 kJ mol^{-1} for (Ia), 119 kJ mol^{-1} for (IIa), and 134 kJ mol^{-1} for (IIIa). The tautomeric preference for (Ia)—(IIIa) to exist in the ketamine form has been shown by ^1H spectroscopy of the ^{15}N-enriched samples.[5] The predominant stabilities of the ketamine forms suggest the difficulty of the 'external' (*cis–trans*) interconversion (*a,b* ⇌ *c,d*), *via* rotation of the *N*-phenylacetoimino-group for the enolimine forms.

In addition, the dipole moment values decreased with increasing stability of the tautomeric forms for the tetramic acid analogues (I)—(III). However, this was not the case for the anilides (Ia)—(IIIa), since the more stable ketamine forms were no longer planar molecules having, rather, a *z* axis factor owing to the phenyl group.

DISCUSSION

If the interconversion for the four tautomers is relatively slow on the ^{13}C n.m.r. time scale, 12 signals might be observed in the carbonyl region for compounds (I)—(III). However, only six carbonyl resonances were observed in the region 168—203 p.p.m. Both co-

incidental overlap of the chemical shifts and/or the predominance of a particular tautomeric form are ruled out by the ^{13}C and ^{1}H spectral evidence,[4] respectively. Therefore, it can be concluded that the rapid prototropic of the tetramic acid analogues (I)—(III) are well explained by electronic theory as resonance hybrids of the ' internal ' tautomers. Table 3 shows the total electron densities and π-electron densities (in parentheses) of

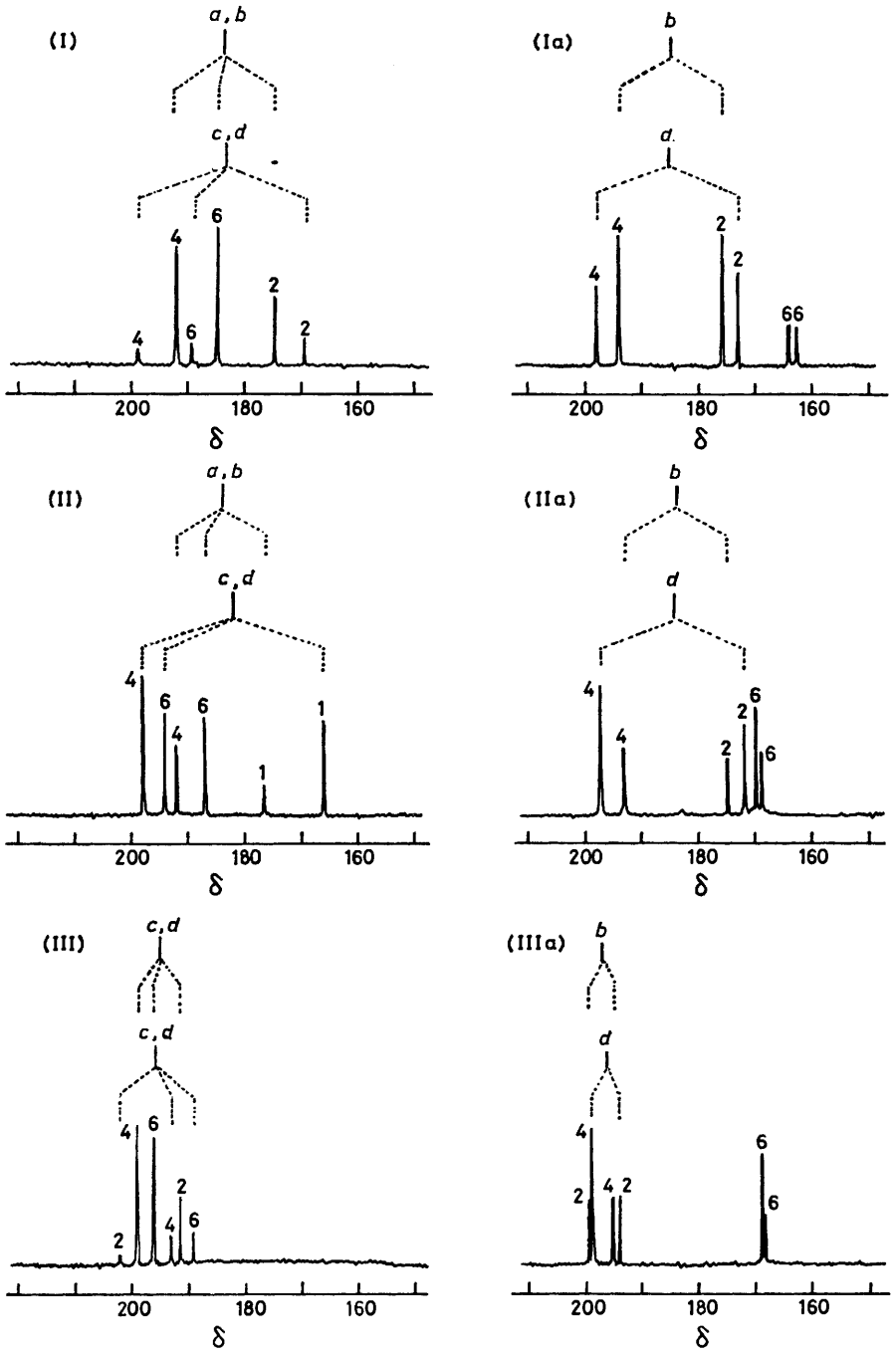


FIGURE The carbonyl region in the ^{13}C spectra of the tetramic acids (I)—(III) and their anilides (Ia)—(IIIa) in $CDCl_3$ at 25.1 MHz and 303 K

interconversion between ' internal ' tautomers on the ^{13}C n.m.r. time scale results in weight-averaged absorbances between them.

The chemical shifts of the carbonyl carbons (C-2,4,6) each carbon atom in these compounds. For compounds (I)—(III), the values calculated by the INDO method for the averaged molecules between *a* and *b*, and *c* and *d*, are presented. π-Electron charge densities of C-2 and C-4

TABLE 3

A.O. population and π-electron densities (parentheses) on carbon atoms in tetramic acid analogues (I)—(III) by INDO and their anilides (Ia)—(IIIa) by CNDO/2 method

Compounds No.	Tautomeric forms	$D_{tot}(D_\pi)$ C-2	C-4	C-6	C-3
(I)	*a,b*	3.6441 (0.8003)	3.7014 (0.7033)	3.6428 (0.7778)	4.2881 (1.3216)
	c,d	3.6472 (0.8552)	3.7445 (0.8085)	3.6470 (0.6880)	4.2888 (1.3232)
(II)	*a,b*	3.5851 (0.7953)	3.6921 (0.6881)	3.6459 (0.7781)	4.2783 (1.3123)
	c,d	3.5946 (0.8858)	3.7306 (0.8174)	3.6465 (0.6798)	4.2883 (1.3287)
(III)	*a,b*	3.7383 (0.8229)	3.6873 (0.8730)	3.6409 (0.7075)	4.3246 (1.4978)
	c,d	3.7509 (0.6861)	3.7061 (0.8179)	3.6911 (0.6892)	4.2761 (1.3246)
(Ia)	*b*	3.6503 (0.7996)	3.7472 (0.7984)	3.7915 (0.7766)	4.2419 (1.2936)
	d	3.6382 (0.7980)	3.7560 (0.7901)	3.7911 (0.7857)	4.2412 (1.3057)
(IIa)	*b*	3.5962 (0.8068)	3.7509 (0.8047)	3.7665 (0.7689)	4.1957 (1.2091)
	d	3.5989 (0.8235)	3.7467 (0.8171)	3.7661 (0.7715)	4.1952 (1.2071)
(IIIa)	*b*	3.7341 (0.7667)	3.7299 (0.7987)	3.8081 (0.7603)	4.1537 (1.2438)
	d	3.7341 (0.7681)	3.7142 (0.8073)	3.8095 (0.7639)	4.1638 (1.2421)

TABLE 4

Calculated π-electron densities of the chelated six-membered ring systems

Compounds	$D_{\sigma\pi}$ *a,b* Form	*c,d* Form
(I)	6.2106	6.1754
(II)	6.0320	6.0643
(III)	6.0004	6.0104
(Ia)	5.9225	5.8872
(IIa)	5.5846	5.6425
(IIIa)	5.6038	5.6407

are varied with their bonding state. With some exceptions, they decrease in the order, enolized carbonyl > free carbonyl > hydrogen-bonded carbonyl, as suggested by classical electronic theory. However, in the enolized state (*b,d* form) electron density of C-6 was shown to be less than in the hydrogen-bonded carbonyl state (*a,c* form). This is explained in the following way. In the *b* and *d* form, C-6 is in the position of a β-olefinic carbon with respect to two carbonyl groups. The resonances of C-6 of the *c,d* form appeared at lower field than those of the *a,b* form. This is supported by the results of the INDO calculation. Table 4 shows that the chelated six-membered ring of the *c,d* form including the lactone (II) and the thiolactone (III) carbonyl group have higher π-electron densities than those of the *a,b* form. As for the 3-acetylteramic acid (I), amide–iminol interconversion might also take place. This decreases the π-electron density of the *c,d* form.

On the other hand, the resonances of the α-olefinic carbons (C-3) of these compounds appeared in the 90—110 p.p.m. region, a field much higher than is usual for olefinic carbons. The explanation for this is that the carbon is located at the α-position to all the carbonyl groups in the molecule, and this has an excess of total- and π-electron densities (Table 3). In the chelate ring of the enol form, the lone-pair electrons on the oxygen atom can take part in π-conjugation, which increases the π-electron density on the olefinic carbon, and results in it being more shielded. Such electron gathering on the α-carbon has been reported for β-diketones.[16]

With respect to the sulphur homologues (III) and (IIIa), unique patterns of the ^{13}C resonances were observed for the thiol-lactone carbonyl carbons (C-2), although the other carbons showed similar chemical shifts and tautomeric separations to the others. The signals of the thiol-lactone carbonyl carbon (C-2) shift *ca.* 20 p.p.m. to lower field compared with those of the lactone (II),(IIa) and amide (I),(Ia) carbonyl carbons (Figure, Table 1). In the case of the nitrogen and oxygen homologues, the charge density at the C-2 carbonyl carbon is increased by the contribution of the electron-releasing mesomeric effect of the adjacent heteroatoms. This results in up-field shifts of the C-2 resonance. The reverse tendency is obvious for the sulphur homologues. The resonances of C-2 in the *a,b* form (free carbonyl) of (III) appeared at lower field (202.7 p.p.m.) compared with that of C-4 in *c,d* form (193.2 p.p.m.). These facts are well explained by comparison of charge densities. Table 5 lists the differences of total-, π-, and δ-electron densities between C-2 and C-4, derived from the data in Table 3. From this Table, it can be concluded that the sulphur atom of the thiol-lactone group plays a double role both as π-electron acceptor and δ-electron donor toward the neighbouring carbonyl group.

It is noteworthy that the separations of the C-2, C-4, and C-6 resonances are very small for (IIIa) (Figure, Table 1). The chemical shift differences for C-6 between the *b* and *d* forms is only 0.2 p.p.m. This indicates that there is no significant difference in their electronic states. This is also supported by the small difference of the π-electron density in the chelated six-membered ring systems (Table 4).

Furthermore, the resonances of the methylene carbon

TABLE 5

Differences of averaged electron densities between C-2 and C-4

Compounds	D_{tot}(C-2) − D_{tot}(C-4)	D_π(C-2) − D_π(C-4)	D_σ(C-2) − D_σ(C-4)
(I)	−0.10 – −0.11	+0.13 – +0.16	−0.10 – −0.12
(II)	−0.09 – −0.15	+0.01 – +0.09	−0.10 – −0.20
(III)	+0.02 – +0.06	−0.01 – −0.03	+0.03 – +0.09
(Ia)	−0.10 – −0.12	0.00 – +0.01	−0.09 – −0.01
(IIa)	−0.15 – −0.16	+0.01 – +0.02	−0.10 – −0.13
(IIIa)	+0.01 – +0.02	−0.01 – −0.02	+0.01 – +0.05

(C-5) for the sulphur homologues (III),(IIIa) appeared at higher field (35—40 p.p.m.) than those of the other homologues (48—75 p.p.m.) (Table 1). This is also supported by the fact that C-5 of (III) and (IIIa) has a higher electron charge density than any other (Table 3). The high electron charge density of C-2 gives rise to a higher reactivity of this position toward electrophilic reagents.[17,18]

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