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The Carbon-13 NMR Spectra of Barbituric-acid Derivatives

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Synopsis. The ^{13}C nuclear magnetic resonance spectra of thirty kinds of barbituric-acid derivatives were measured, and the chemical shifts of each carbon were assigned. The correlation between chemical shifts of the ring skeletal carbon and the pK_a values was examined.

There have been several reports concerning the ^{13}C nuclear magnetic resonance (NMR) spectra of barbituric-acid derivatives. Okada *et al.*[1] have measured the ^{13}C NMR spectra of some 5-monosubstituted barbituric-acids (I). They pointed out that (I) dissociated by releasing the hydrogen at the 5-position and that there was a good linear correlation between the ^{13}C chemical shifts of C-5 and the pK_a values. In 5,5-disubstituted and 1-methyl-5,5-disubstituted barbituric-acids (II) and (III), however, dissociation may be more complicated, as is shown in Chart 1. In order to gain a clew with regard to those dissociation schemes, we tried to assign the chemical shifts of each carbon for (II) and (III) and examined the correlation of the ^{13}C shifts of the ring skeletal carbons with the pK_a values of these compounds.

Experimental

Materials. The barbituric-acids used for the measurement of the ^{13}C NMR spectra are listed in Table 1. Compounds **2**, **3**, **7**, **9**, **10**, **11**, **13**, **14**, **28**, and **29** were synthesized by the methods described in the literature.[2,3] Compound **30** was synthesized by the methylation of **15** with CH_2N_2. The other compounds were those reported in the preceeding paper.[4]

Measurements of the Acid-dissociation Constants and the ^{13}C NMR Spectra of Barbituric-acid Derivatives. The apparent acid-dissociation constants, pK_a, were determined by means of a Hitachi model UV-200 spectrophotometer at 20 °C in an ionic strength of 0.75. The pK_a values of the new compounds were as follows : **2**=7.94, **3**=7.85, **7**=8.14, **9**=7.53, **10**=8.05, **11**=7.77, **13**=7.87, **14**=7.61, **28**=7.85, and **29**=7.90. The ^{13}C NMR spectra were measured at room temperature by means of a NEVA NV-21 (22.6 MHz) spectrometer. All the samples were dissolved in dimethyl-d_6 sulfoxide (1M). The chemical shifts were expressed in ppm downfield from tetramethylsilane (TMS).

Results and Discussion

Table 1 shows the ^{13}C chemical shifts of the ring skeletal carbons, assigned by using the off-resonance technique or by comparing them with the values in the literature.[1,5] The mean value of the chemical shifts of *N*-methyl carbon for (III) was given as 27.09 ± 0.25 ($n=15$).

We attempted to correlate the ^{13}C shifts with the pK_a values as follows. The results of regression analyses concerning Eq. 1 are summarized in Table 2.

$$pK_a = a_0 + a_1\delta_c(\text{ring position}), \quad (1)$$

where δ_c indicates the ^{13}C shift of the ring skeletal

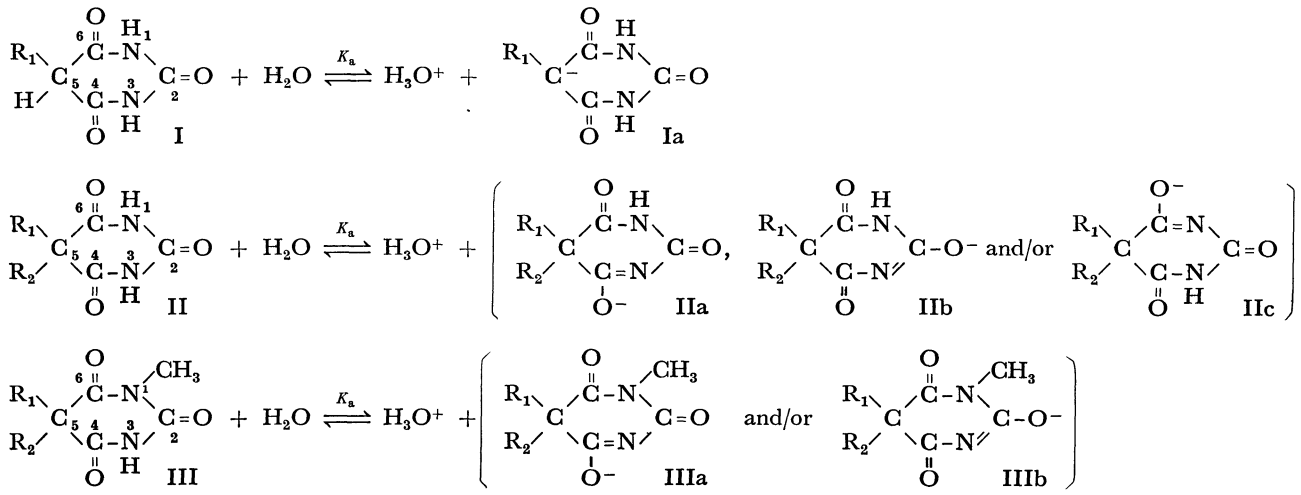


Chart 1.

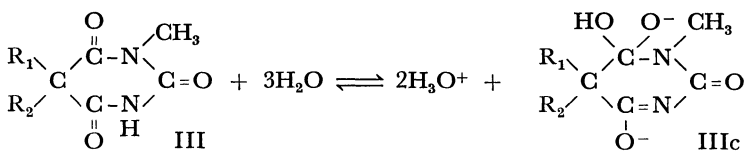
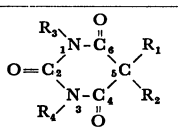


Chart 2.

Table 1. Compound number and ^{13}C chemical shift (δ_C) in ppm of barbituric-acid derivatives

Compound No.	Substituent[a]		δ_C[b]				
			Ring				N-CH_3
	R_1	R_2	C-2	C-4	C-6	C-5	
II, (R_3=R_4=H) series							
1	Ethyl	Ethyl	150.0	173.1×2		56.6	
2	Ethyl	Allyl	149.8	172.4×2		55.8	
3	Ethyl	Propyl	149.9	173.1×2		55.9	
4	Ethyl	3-Methylbutyl	149.9	173.1×2		55.8	
5	Ethyl	1-Methylbutyl	150.1	(173.1)	(172.8)[c]	59.3	
6	Ethyl	Cyclohexen-1-yl	150.0	171.5×2		61.5	
7	Ethyl	Cyclohexyl	150.1	172.7×2		59.5	
8	Ethyl	Phenyl	149.9	171.6×2		60.0	
9	Ethyl	Benzyl	149.4	172.5×2		57.8	
10	Ethyl	α-Methylbenzyl	149.4	(172.8)	(171.7)[c]	60.1	
11	Ethyl	Cinnamyl	149.3	(172.4)	(171.6)[c]	57.7	
12	Allyl	Allyl	149.7	171.9×2		55.1	
13	Propyl	Propyl	149.8	173.2×2		55.2	
14	Benzyl	Benzyl	148.9	172.1×2		59.1	
III, (R_3=CH_3, R_4=H) series							
15[d]	Ethyl	Ethyl	149.9	171.8	171.3	56.9	27.1[e]
16	Ethyl	Allyl	149.8	171.4	170.8	56.2	27.1
17	Ethyl	Propyl	149.8	171.9	171.3	56.2	27.1
18	Ethyl	3-Methylbutyl	149.8	171.9	171.3	56.1	27.1
19	Ethyl	1-Methylbutyl	150.0	171.8	171.2	59.7	27.1
20	Ethyl	Cyclohexen-1-yl	149.9	170.5	169.8	61.7	27.4
21	Ethyl	Cyclohexyl	150.6	172.1	171.5	60.3	26.8
22	Ethyl	Phenyl	149.8	170.4	169.9	60.3	27.6
23	Ethyl	Benzyl	149.3	171.4	170.8	58.3	27.0
24	Ethyl	α-Methylbenzyl	149.7	172.0	170.5	61.0	27.0
25	Ethyl	Cinnamyl	150.2	171.9	171.2	56.9	27.4
26	Ethyl	Phenylpropyl	150.2	172.4	171.8	56.3	27.2
27	Allyl	Allyl	149.6	170.8	170.1	55.4	27.0
28	Benzyl	Benzyl	149.1	171.5	170.7	59.7	26.8
29	Benzyl	α-Methylbenzyl	149.2	171.4	170.3	61.8	26.6
IV, (R_3=R_4=CH_3) series							
30	Ethyl	Ethyl	150.9	171.4×2		57.4	28.2×2



a) b) Symbol "×2" means twice the intensity. c) In Compounds **5**, **10**, and **11**, which have no *N*-methyl group, equivalent signals of carbons at the 4- and 6-positions split off in two. d) The δ_c 171.8 is the signal to C-4, and the δ_c 171.3 is that to C-6, which is situated nearer the *N*-methyl group. In **1**, δ_c 173.1×2 is assigned as the signals to C-4 and C-6. In **30**, these signals appear at a higher field, δ_c 171.4×2. e) The ^{13}C signal of the *N*-methyl group was shown as a quartet in the partial proton-decoupling state.

carbons for (II) and (III), and where a_0 and a_1 are constants. In a series of (II), it was found that the regression of pK_a with δ_c (4 and/or 6 position) was significant at the 5% level concerning the F-test for the variance ratio, as is shown in Eq. 3. On the other hand, the regression of pK_a with δ_c(2) or of pK_a with δ_c(5) was less significant, as is shown in Eq. 2 or Eq. 4. Thus, the ionization of (II) may produce (IIa) and/or (IIc). Further, in the (III) series, the regression of pK_a with δ_c(4) was highly significant,

Table 2. Regression analyses[a] between pK_a and δ_c of ring carbon for two barbituric-acid derivatives, (II) and (III)

Series	a_0 +	a_1 (t value)	δ_c	γ Correlation coeff.	Ve Variance	$F_{1,n-2}$ Variance ratio	Equation
II	−8.06	0.106(0.52)	δ_c(2)	0.149	0.066	0.274	2
	−41.4	0.285(2.92*)	δ_c(4 and/or 6)	0.697	0.038	8.49*	3[b]
	9.28	−0.026(0.80)	δ_c(5)	0.224	0.064	0.632	4
III	−15.06	0.153(1.09)	δ_c(2)	0.291	0.044	1.20	5
	−44.21	0.304(5.36**)	δ_c(4)	0.830	0.015	28.8**	6
	−30.25	0.223(3.17**)	δ_c(6)	0.666	0.026	10.4**	7
	7.85	0.001(0.02)	δ_c(5)	0.006	0.048	0.001	8

a) pK_a=a_0+$a_1\delta_c$ (ring position). b) No. of samples: n=11 (No. **1**—No. **14** except Nos. **5**, **10**, and **11**). Symbol ** indicates a substance to be significant at the 1% level, *, to be significant at the 5% level.

as had been expected (Eq. 6), while that of pK_a with δ_c(2) or of pK_a with δ_c(5) had little significance (Eq. 5 or Eq. 8). The regression of pK_a with δ_c(6) was also significant at the 1% level relative to the F-test (Eq. 7). It seems that this result is inconsistent with Chart 1. In this connection, Eriksson *et al.*[6] have reported that a tetrahedral substrate–hydroxide ion complex of 1-methylbarbituric-acid was formed in an alkaline solution. Accordingly, the ionization form (IIIc) shown in Chart 2 may be useful in predicting a good correlation of Eq. 7. A complete explanation must be left to further study because pK_a is related to the ^{13}C chemical shifts at the 4 and/or 6 position of 5,5-disubstituted barbituric-acid derivatives.

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