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Intramolecular Interactions II[1]

Weak Intramolecular Interactions in Derivatives of Barbituric Acid

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A weak intramolecular interaction has been found between an *N*,*N*-dimethylbarbituric acid ring and an aromatic system connected by an aliphatic chain, and has been studied by UV-VIS and NMR spectroscopy. ΔH and ΔS values have been determined from the temperature dependence of chemical shifts.

(Keywords: N,N-dimethylbarbituric acid; ^{1}H-*NMR; UV-VIS-spectra)*

Intramolekulare Wechselwirkungen II.
Schwache intramolekulare Wechselwirkungen in Barbitursäurederivaten

Eine schwache intramolekulare Wechselwirkung zwischen *N*,*N*-Dimethylbarbitursäure und einem mit ihr über eine aliphatische Kette verbundenen aromatischen Ring wurde mittels UV-VIS- und NMR-Spektroskopie untersucht. Aus der Temperaturabhängigkeit der chemischen Verschiebung wurden die thermodynamischen Daten der Wechselwirkung bestimmt.

Introduction

Attractive forces between aromatic systems and systems with π-electrons have been described by several authors[2–5]. Strong (charge transfer) interactions as well as molecular aggregates have been studied. The importance of such complexes in biological systems (e.g. conformation of peptides, proteins and nucleic acids) has induced several investigations in this field[6–8]. Few model compounds have been

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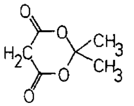
synthesised to study intramolecular interactions with spectroscopic methods[9–21]. Intramolecular excited-state interactions have been also investigated[22–25].

Weak attractive forces cause, per example, rotational hindrance in diketopiperazines[15–20]. Similar associates have been observed in aryl substituted derivatives of the cyclic acylal of malonic acid ("*Meldrum*'s acid") (**1**)[29].



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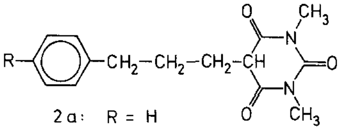
ΔH-values depending on various substituents have been estimated by means of NMR experiments[21]. In order to study such weak intramolecular interactions we have prepared several compounds containing an *N*,*N*-dimethylbarbituric acid system and an aromatic ring connected by a saturated carbon atom chain.



2a: R = H

b: R = CH_3

c: R = OCH_3

d: R = NO_2

Electron absorption spectroscopy and NMR spectroscopy have been used to investigate the behavior of these compounds in solution.

Results and Discussion

Electron Absorption Spectra

Electron absorption spectroscopy is a common tool for the investigation of strong inter- and intramolecular interactions especially if charge transfer phenomena are included. Weak π—π-interactions on the other hand do not change the UV spectra drastically and cannot be observed that way. The electron absorption spectra of **2 a**-**d** in aqueous solution are strongly *pH* dependent. At low *pH* the UV-VIS spectrum is

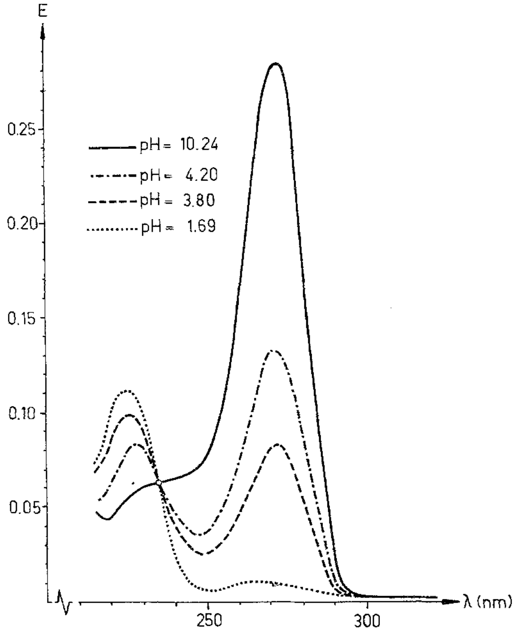


Fig. 1. UV spectra of *n*-propyl-*N*,*N*-dimethylbarbituric acid at various *pH* values

Table 1. *ε-values of* **2c** *at various concentrations*

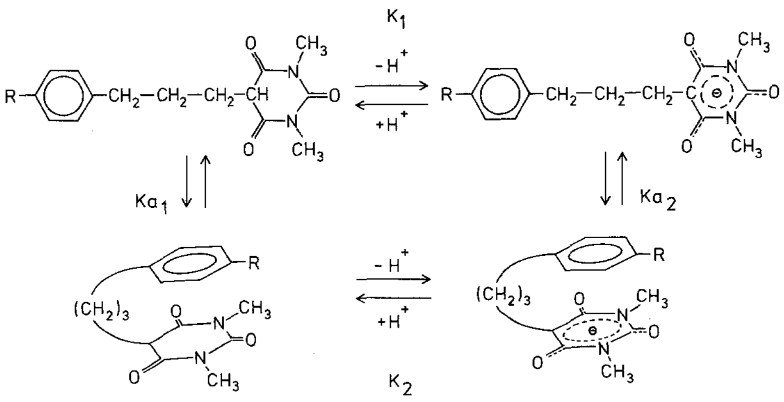
c (mol l^{-1})	ε (l mol^{-1} cm^{-1})
$2 \cdot 10^{-2}$	1785
$2 \cdot 10^{-3}$	1772
$2 \cdot 10^{-4}$	1786
$2 \cdot 10^{-5}$	1778

a superposition of the absorption of the aromatic ring and the heterocyclus, whereas at higher *pH* the spectrum is dominated by the absorption of the *N*,*N*-dimethylbarbituric acid anion at 262 nm. There is almost no indication for any charge transfer bands over the whole *pH* range. The *pH*-dependence of the UV-VIS-spectra of the *N*,*N*-dimethyl barbituric acid chromophor only is shown in Fig. 1. Fig. 1 shows also a clear definded isosbestic point which is an indication for an equilibrium between two molecular species. To estimate the importance of intermolecular association we have measured the concentration dependence of the electron spectra of **2a**–**d**. As one can see from Table 1, the ε-values do not vary in the concentration range from 10^{-2}-10^{-5} mol/l thus showing that contributions from intermolecular association processes are neglegible in this concentration range. From the *pH* dependence of the extinction at a certain wavelength the *pK* values of the neutralisation can be calculated. Table 2 gives the *pK* values of **2a**–**d** determined at several wavelengths. The *pK* values of **2a**–**c** are comparable to the corresponding acidity constant of *n*-propyl-*N*,*N*-dimethylbarbituric acid, whereas the *pK* of **2d** is significantly lower. Thus the nitro-substituent influences the acidity of the heterocyclus even if both are separated by the aliphatic chain. Inductive effects are practically not transmitted via an *n*-propyl chain and therefore the enhanced acidity could be explained by a stronger association of the electron deficient system.

Table 2. *pK-values of* **2a**–**d** *and* **3a**–**b** *in aqueous ethanolic solution*

Compound	*pK*
2a	4.2
2b	4.3
2c	4.3
2d	3.7
3a	4.5
3b	4.4

Scheme 1

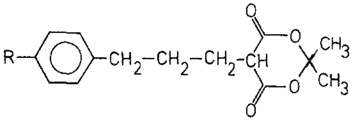


From reaction scheme 1 one can deduce that different association constants Ka_1 and Ka_2 cause also different acidity constants K_1 and K_2 ($Ka_2 : Ka_1 = K_2 : K_1$). The overall pK will be also changed in such a case.

Table 3. *Chemical shifts of protons A-G in* **2a**-**d** *(in ppm)*

Compound	δ_A	δ_B	δ_C	δ_D	δ_E	δ_F	δ_G
2a			2.64	1.63	2.13	3.43	3.27
2b			2.59	1.60	2.11	3.42	3.27
2c	6.75	7.02	2.57	1.59	2.10	3.41	3.27
2d	8.13	7.36	2.80	1.72	2.17	3.45	3.28

The associative interactions of an aromatic system and "*Meldrum's* acid" are somewhat weaker than for barbituric acids; a diminished or even unmeasureable effect for compounds **3a** and **3b** would be expected[28].

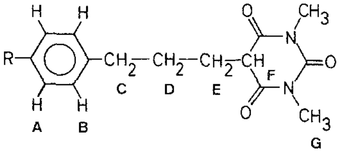


3a: R = $-OCH_3$
3b: R = $-NO_2$

In addition Table 2 presents the pK values of **3a** and **3b**, showing more or less constant values for the acidity. In these compounds the (weaker) intramolecular association seems to be similar for the anion as well as for the neutral molecule.

Nuclear Magnetic Resonance Spectra

The ^1H-NMR spectra of **2a**-**d** show clearly separated signals of the protons in position C to F (Table 3), a singulett which is assigned to the $N-CH_3$ groups and different multipletts corresponding to the aromatic protons.



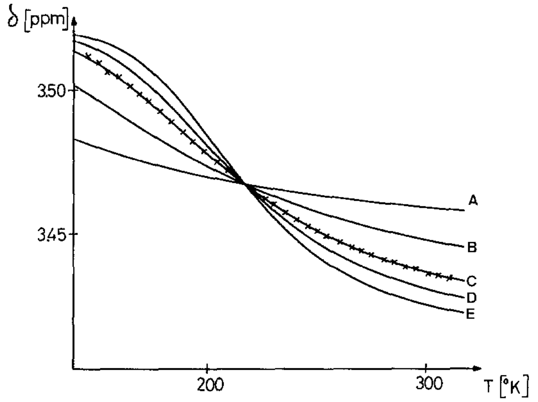
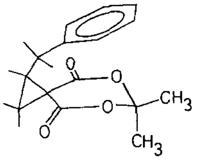


Fig. 2. Theoretical and experimental temperature dependence of the chemical shift of proton F in compound **2d** (*A* $\Delta H = 2$ kJ/mol, *B* $\Delta H = 5$ kJ/mol, *C* $\Delta H = 8.6$ kJ/mol, *D* $\Delta H = 11$ kJ/mol, *E* $\Delta H = 14$ kJ/mol)

Table 4. ΔH, ΔS *and* T_w *(*$K = 1$*) values of* **2a**-**d** *estimated from temperature dependent NMR experiments*

Compound	ΔH (kJ/mol)	ΔS (J/°C · mol)	T_w (°C)
2b	2.0 ± 0.4	9.2 ± 2.0	218 ± 15
2c	1.8 ± 0.3	9.0 ± 2.0	200 ± 15
2d	2.4 ± 0.4	12.2 ± 3.0	197 ± 15

The resonance frequencies of the protons in the aliphatic chain and the N—CH_3 groups (position A to D) are temperature dependent. Fig. 2 gives the temperature dependence of **2d**. We have measured NMR spectra from 20 °C to —100 °C in steps of 5 °C. From these measurements ΔH of the association process has been calculated. The results of this analysis are given in Table 4. These values are mean values derived from the temperature dependent shifts of several protons in the same molecule. The obtained ΔH values show that the intramolecular interaction between the aromatic ring and the heterocyclic system is relatively weak (between 7.5 and 10.0 kJ/mol). The association enthalpy for **2d** seems to be the largest one. The ΔS values are in the order of 35-50 J/deg mol. They are significantly higher than the values obtained for a similar but more sterically hindered system[21] (ΔS = 10-20 J/deg mol).



With these experiments it has been demonstrated, that a weak intramolecular interaction exists between the *N*,*N*-dimethylbarbituric acid and the aromatic ring system. There is no indication for charge transfer phenomena.

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Experimental

Compounds **2a**-**c** were synthesised by a modified procedures already described in the literature, using the method of *Braun* and *Kruber*[26] for the preparation of the *para*-substituted derivatives of 3-phenylpropyl malonic acid and the method of *Clark-Lewis* and *Thompson*[27] for the ring closure (yields given).

2a: $C_{15}H_{18}N_2O_3$; m.p. 98 °C; yield: 31.1% recr. from acetone.

Analysis: calc.: C 65.7, H 6.6, N 10.2;
found: C 65.6, H 6.5, N 10.3.

2b: $C_{16}H_{20}N_2O_3$; m.p. 86-88 °C; yield: 51.0%; recr. from ethanol.

Analysis: calc.: C 66.7, H 6.9, N 9.7;
found: C 66.5, H 6.8, N 9.7.

2c: $C_{16}H_{20}N_2O_4$; m.p. 82-83 °C; yield: 17.1%; recr. from ethanol.

Analysis: calc.: C 63.2, H 6.6, N 9.2;
found: C 63.3, H 6.4, N 9.1.

Compound **2d** was synthesised by nitration of 3-phenylpropyl malonic acid, followed by ring closure according to the procedure described above.

Preparation of 3-(4-nitro)-phenylpropyl malonic acid: 50 mmol (11.1 g) of 3-phenylpropyl malonic acid was dissolved in a minimum quantity of a mixture of acetic acid and acetic anhydride (1 : 1). A mixture of 6 ml concentrated sulfuric acid and 5 ml concentrated nitric acid was added, the temperature maintained between 10° and 15 °C. After the addition, the reaction mixture was kept at room temperature for 12 h, afterwards poured on ice and filtered off by suction. The product was washed with ligroin several times and dried in vacuo.

$C_{12}H_{13}NO_6$; m.p. 153-155 °C; yield: 30.3%.

Analysis: calc.: C 53.9, H 4.9, N 5.2;
found: C 53.6, H 4.8, N 5.0.

2d: $C_{15}H_{17}N_3O_5$; m.p. 128-130 °C; yield: 41.8%; recr. from ethanol.

Analysis: calc.: C 56.4, H 5.3, N 13.2;
found: C 56.1, H 5.3, N 13.0.

UV-VIS spectra were recorded on a Perkin-Elmer spectrophotometer 330. The temperature was kept constant at 25 °C within 0.1 °C. The solutions used for the measurements were prepared in water, containing 20% of ethanol for solubility reason. The *pH* was adjusted by various buffer solutions and was controlled with a glass electrode. The *pK* values were estimated by fitting a theoretical curve to the experimental points by a computer program.

The NMR spectra were recorded on a Bruker WM 250 NMR spectrometer with a variable temperature unit. The thermodynamic parameters were calculated by a method described before[21].

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