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^{15}N-NMR-Studies on the Neutralization Reaction of Arylidene Dimethyl Barbituric Acids Organic *Lewis* Acids 38[1]

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The ^{15}N-NMR-spectra of benzylidene *N,N'*-dimethyl barbituric acid and *p*-chloro-benzylidene *N,N'*-dimethyl barbituric acid have been measured together with their addition products with piperidine and morpholine. The *Lewis* Acid reactivity is discussed in terms of ^{15}N-chemical shifts.

(Keywords: Benzylidene N,N'-dimethyl barbituric acid; Organic Lewis acids; ^{15}N-NMR-spectroscopy; Piperidine; Morpholine)

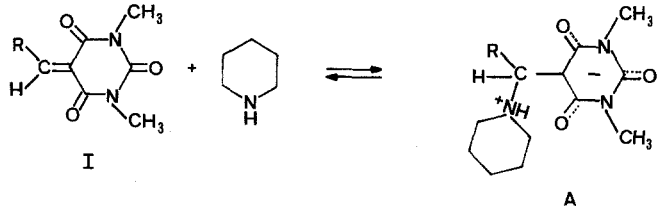
^{15}N-NMR-Untersuchungen über die Neutralisierungsreaktion von Arylidendimethylbarbitursäuren. Organische Lewis-Säuren 38

Die ^{15}N-NMR-Spektren von Benzyliden-*N,N'*-dimethylbarbitursäure und *p*-Chlorbenzyliden-*N,N'*-dimethylbarbitursäure und deren Additionsprodukte mit Piperidin und Morpholin wurden gemessen und im Hinblick auf die *Lewis*säureaktivität dieser Substanzklasse interpretiert.

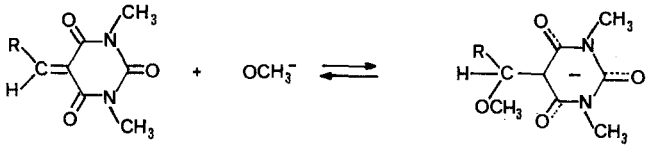
Introduction

The reactivity and spectroscopic properties of compounds with polar C=C double bonds have been the subjects of various investigations[1]. Especially the condensation products of 1,3-diketo compounds in which the two carbonyl groups are forced into a coplanar or almost planar steric arrangement (e.g. *N,N'*-dimethyl barbituric acid) with aromatic aldehydes show an interesting behavior towards nucleophilic attack. These substances undergo neutralization reactions, adding bases like methoxide or neutral nitrogen or phosphorous bases[2—7] reversibely.

The negative charge in the zwitterion (A) or in the anion (B) is efficiently delocalized within a planar extended π-electron system. This powerful stabilization leads in protic solvents to acidity constants which are similar to *Bronsted* acids: benzylidene *N,N'*-dimethyl barbituric acid $pK_a = 9.17$[8], benzoic acid $pK_a = 9.48$. Compounds of type I act therefore as "electrically neutral organic *Lewis* acids". The reactivity and the spectroscopic properties of these "cryptic" *Lewis* acids have been studied widely[1, 3–9].



I A



B

^{1}H-NMR-spectra have been performed as a part of a study of the stereochemistry[9, 10], ^{13}C-NMR-spectra have been reported[11] and a kinetic analysis of the *Lewis* acid neutralization reaction has been performed in protic[12–14] and in aprotic solvents[15].

In order to study the neutralization reaction of benzylidene *N,N'*-dimethyl barbituric acid (I) with nitrogen bases we have measured ^{15}N-NMR-spectra of I and of the addition products with piperidine and morpholine.

Experimental

Benzylidene *N,N'*-dimethyl barbituric acids and its *para*substituted derivatives were prepared and purified according to procedures described in the literature[9]. Piperidine and morpholine were freshly distilled from CaH_2 under argon atmosphere. $CDCl_3$ (99.5%, Uetikon) was dried by chromatography (Al_2O_3).

The natural abundance ^{15}N-NMR-spectra were obtained at a frequency of 25.36 MHz with a BRUKER WM-250 NMR-spectrometer equipped with an 80 K ASPECT-2000 computer. All spectra were obtained with 5 ml of a 0.8 molar solution of compounds in $CDCl_3$ using 15 mm tubes. Nitrogen base concentration of 0.8 and 2.0 mol/l were used. The deuterium resonance of the solvent provided the field-frequency lock. A 5 mm concentric tube containing CH_3NO_2 was used as external reference standard.

Typical aquisition parameters are: number of scans 2 000–50 000, 32 K data points, sweep width 12 KHz, pulse width 10 μs (15° flip angle), pulse interval 1.5 s, digital resolution 0.7 Hz.

Proton noise decoupling was employed (1 W rf power) during the measurement giving NOE enhanced ^{15}N-resonances.

The sample temperature was 35 °C. The reproducibility of chemical shifts is about $\pm$ 0.1 ppm.

Results and Discussion

The nitrogen-15 chemical shifts obtained for benzylidene *N,N'*-dimethyl barbituric acid and two of its derivatives are listed in Table 1 in comparison to selected ^{1}H- and ^{13}C-chemical shifts. Nitrogen lone pair delocalization by the π-electron system of the adjacent carbonyl groups deshields the nitrogen nuclei drastically. Therefore the absorption of the ^{15}N nuclei of barbituric acid ($\delta_N = 227.8$ ppm)—referred to nitromethane[16]—is shifted downfield compared to amides (e.g. dimethylformamide $\delta_N = 278.4$ ppm) but consistently shielded in comparison to imides (e.g. the cyclic imide of glutaric acid, $\delta_N = 206.0$ ppm[16]). The ^{15}N-nuclei of barbituric acids reflect properties of both imides and urea nitrogens (urea, $\delta_N = 305.2$ ppm). N-methylation of the heterocyclic ring shields the nitrogen nuclei (*N,N'*-dimethyl barbituric acid: $\delta_N = 233.4$ ppm). In arylidene *N,N'*-dimethyl barbituric acid the C=C double bond substituted with an aromatic ring leads to low frequency shifts of both N-atoms (Table 1), which due to the geometry of the molecule are not identical anymore. Different substitution at the aromatic ring produces only slight changes in the ^{15}N resonance positions. In comparison to ^{1}H- and ^{13}C-chemical shifts (Table 1) ^{15}N-chemical shifts seem to be more sensitive than ^{13}C-chemical shifts toward changes in electron density in the heterocyclic ring caused by different substituents; only the ^{13}C-chemical shifts of C-5 and C-6 belonging to the C=C double bond appear to exert effects on the aromatic substitution. Addition of the nitrogen base piperidine or morpholine to compounds of type I changes the ^{15}N-NMR-spectra completely. Fig. 1 shows the ^{15}N-NMR-spectrum of the addition product of benzylidene *N,N'*-dimethyl barbituric acid and morpholine. Both signals of the free morpholine and morpholine bound to the *Lewis* acid can be observed showing slow exchange rate on the NMR time scale. In

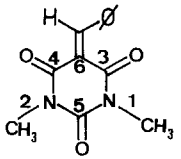


Table 1. ^{1}H-, ^{13}C-, ^{15}N-*Chemical shifts of some arylidene N,N′-dimethyl barbituric acids; chemical shifts in ppm;* ^{1}H, ^{13}C *chemical shifts: tetramethylsilan as reference;* ^{15}N *chemical shifts relative to external, neat nitromethane*

Compound	H_1 [a]	H_2 [a]	$C_{1,2}$	C_3 [b]	C_4 [b]	C_5	C_6	$N_{1,2}$
N,N′-dimethyl barbituric acid								
Benzylidene-	3.38	3.42	28.4/29.2	160.3	162.4	151.4	117.6	235.1/237.2
p-Chlorobenzylidene-	3.38	3.42	28.5/29.1	160.4	162.3	151.1	118.0	234.8/237.0
p-Bromobenzylidene-	3.37	3.42	28.5/29.1	160.5	162.5	151.0	118.1	234.4/236.6

[a] Assignment by shift reagents[9].
[b] Assignment by C—H-long range coupling[10].

Table 2 the ^{15}N-chemical shifts of the association products between benzylidene *N,N'*-dimethyl barbituric acid and piperidine and morpholine are listed: The nitrogen nuclei of the anion are equivalent and their absorption is shifted upfield caused by the negative charge within the heterocyclic ring. The ^{15}N-chemical shifts do not seem to depend on the substituents at the aromatic ring nor to the adjacent nitrogen base. On the other hand the nitrogen nuclei of the nitrogen base are shifted considerably.

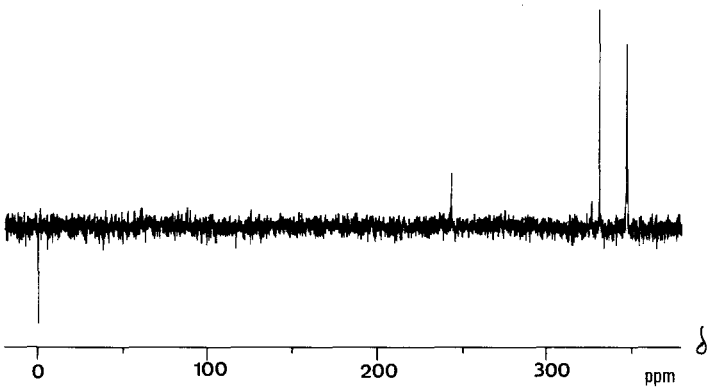


Fig. 1. ^{15}N-NMR-Spectrum of the addition product of benzylidene *N,N'*-dimethyl barbituric acid and morpholine (solvent $CDCl_3$, reference nitromethane)

The addition of the base to the electrophilic center of the *Lewis* acid followed by the delocalization of the negative charge causes a strong deshielding of about 18 ppm. N-alkylation of piperidine with residues with more than one carbon atom leads to similar changes in chemical shifts[17, 18]: piperidine $\delta_{N1} = 342.1$ ppm, *N*-methylpiperidine $\delta_{N2} = 340.8$ ppm, *N*-ethylpiperidine $\delta_{N3} = 329.4$ ppm; $\Delta\delta_{N1,N3} = 12.7$ ppm. The positive charge of the nitrogen nuclei produces a downfield shift, but somewhat smaller[19]: piperidine-hydrochloride $\delta_{N1'} = 337.2$ ppm, $\Delta\delta_{N1N1'} = 4.9$ ppm; *N*-ethyl-piperidine-hydrochloride $\delta_{N3'} = 325.8$ ppm, $\Delta\delta_{N3N3'} = 3.6$ ppm. It seems reasonable that the shift difference of the free piperidine and piperidine associated nitrogens is a superposition of both effects. The nitrogen nuclei of morpholine behaves similar; a downfield shift of 16.0 ppm is observed.

In spectra of solutions in which nitrogen base is in excess (2.5 fold) signals of the free amine can be also observed. In the case of the addition product with morpholine a concentration dependence of the ^{15}N-NMR-absorption appears, attended by a slight line broadening. The reason for this is that the symmetrical chemical exchange process (*Lewis*

Table 2. ^{15}N *Chemical shifts of the association products of some arylidene N,N'-dimethyl barbituric acid with piperidine and morpholine; solvent* $CDCl_3$, *chemical shifts in ppm, neat nitromethane as external reference*

Acid	Base	$N_{heterocycle}$	$N_{base/bound}$	$N_{base/free}$	Concentration ratio
N,N'-dimethyl barbituric acid					
Benzylidene-	Piperidine	243.9	324.2		1:1
Benzylidene-	Piperidine	243.9	324.2	342.0	1:2.5
Benzylidene-	Morpholine	243.9	327.6		1:1
Benzylidene-	Morpholine	243.8	331.8	347.8 (350.1)[17]	1:2.5
p-Chlorobenzylidene	Piperidine	243.6	324.2	341.7	1:2.5

Acid·Base) + base′ $\overset{k}{\rightleftarrows}$ (*Lewis* Acid·Base′) + base is faster if base = base′ = morpholine. The rate constant k is mainly determined by the dissociation rate constant k_{21} *Lewis* Acid + base $\underset{k_{21}}{\overset{k_{12}}{\rightleftarrows}}$ (*Lewis* Acid·Base) [k_{21} (piperidine): $2.7\,s^{-1}$; k_{21} (morpholine): $20\,s^{-1}$; solvent CH_3CN, temperature $T = 25\,°C$][15]. The ^{15}N-NMR-spectra reveal that in the addition product the nitrogen base is bound to the *Lewis* acid via an C—N bond and a positive charge remains at the nitrogen nuclei. Moreover the lifetime of the associate is relative long on the NMR time scale.

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