SUBSTITUENT EFFECT ON ACIDITY OF SUBSTITUTED 2-(4-NITROBENZOYLAMINO)ALKANAMIDES IN METHANOL–DIMETHYL SULFOXIDE MIXTURES

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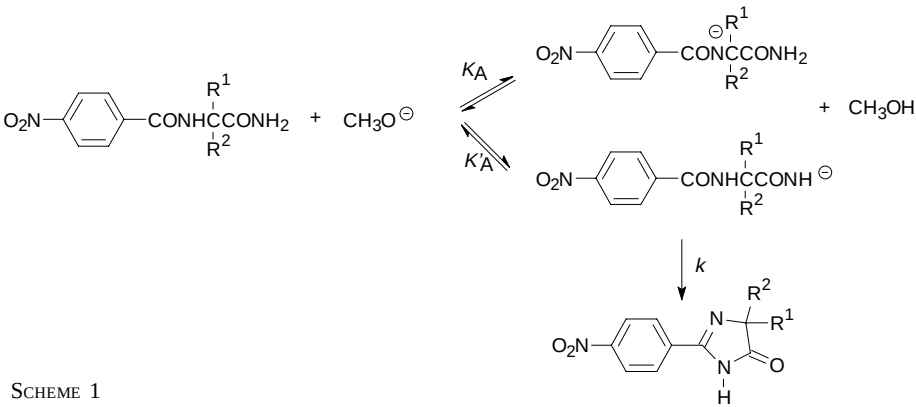
Received August 13, 1997
Accepted October 20, 1997

Dedicated to Professor Vojeslav Sterba on the occasion of his 75th birthday.

The dissociation constants of substituted 2-(4-nitrobenzoylamino)alkanamides, *N*-[2-(4-nitrobenzoylamino)alkanoyl]pyrrolidines, and *N*-alkyl-4-nitrobenzamides have been measured spectrophotometrically in 60 and 80% v/v DMSO. The pK_A values of these *N*-acids are discussed from the point of view of substituents at the acetamide α-carbon atom.

Key words: Dissociation constants; Substituent effects; 2-(4-Nitrobenzoylamino)alkanamides; Solvent effects; Steric effects.

The substituted 2-(4-nitrobenzoylamino)alkanamides contain two dissociation centres in their molecules, *viz.* the benzamide and acetamide ones, and they were used as intermediates in syntheses of imidazolinone derivatives in MeOH–DMSO media[1]. This cyclization reaction, whose kinetics is described in ref.[1], is base catalyzed and its rate-limiting step is ionisation of the substrate (Scheme 1). It is only the anion formed



SCHEME 1

by the ionisation at the acetamide centre, which can provide the cyclization reaction product (the respective substituted derivative of imidazolinone).

The aim of the present communication was to find out the way in which substituents (R^1, R^2) at the acetamide α-carbon atom affect the acidity of the benzamide and acetamide centres in the molecules of substituted 2-(4-nitrobenzoylamino)alkanamides, and which of the nitrogen atoms of the substrates is preferably deprotonated and what is the proportion of individual anions in their mixtures in MeOH–DMSO media.

EXPERIMENTAL

The temperature data have not been corrected. The ^{1}H NMR spectra were measured on an AMX 360 Bruker spectrometer at 360.14 MHz at 25 °C in deuteriochloroform and hexadeuteriodimethyl sulfoxide. The chemical shifts have been referenced to the signals of the nondeuteriated solvents ($\delta(^1H)$ 7.25 $CHCl_3$ and $\delta(^1H)$ 2.55 DMSO). The electronic spectra were measured on a Hewlett–Packard 8453 Diode Array apparatus at 25 °C.

Chemicals

Methanol p.a. (Aldrich) was redistilled under argon and kept in a bottle with molecular sieve A4. Dimethyl sulfoxide p.a. (Aldrich) was kept in a bottle with molecular sieve A4. The water content (according to Fischer) was 0.09–0.12% w/w. Sodium methoxide was prepared as a 5 M solution by dissolving sodium metal in methanol which had been rid of carbon dioxide by distillation under argon. The solutions of definite concentration were prepared by diluting with methanol, and their MeONa concentration was determined by means of titration with a standard solution of hydrochloric acid. The MeOH–DMSO solutions with MeONa concentrations above 5 mol l^{-1} were prepared by dissolving solid MeONa (Aldrich) in MeOH–DMSO mixtures, and their MeONa concentration was determined as above.

N-Acids: *N*-(4-nitrobenzoylamino)pyrrolidine (**1a**), *N*-[2-(4-nitrobenzoylamino)propanoyl]pyrrolidine (**1b**), *N*-[2-(4-nitrobenzoylamino)-3-methylbutanoyl]pyrrolidine (**1c**) and *N*-[2-(4-nitrobenzoylamino)-2-methylpropanoyl]pyrrolidine (**1d**) were prepared from the corresponding amino acids, which were esterified (methanol and gaseous hydrogen chloride), then acylated with 4-nitrobenzoyl chloride in chloroform, and finally aminolyzed[2] with pyrrolidine. The adopted 2-(4-nitrobenzoylamino)ethanamide (**2a**), 2-(4-nitrobenzoylamino)propanamide (**2b**), 2-(4-nitrobenzoylamino)-3-methylbutanamide (**2c**), 2-(4-nitrobenzoylamino)-2-methylpropanamide (**2d**), 2-(4-nitrobenzoylamino)-2,3-dimethylbutanamide (**2e**), 1-(4-nitrobenzoylamino)-1-cyclohexanecarboxamide (**2f**), 2-(4-nitrobenzoylamino)-2-phenylpropanamide (**2g**), 2-(4-nitrobenzoylamino)-2,4-(nitrophenyl)propanamide (**2h**), and 2-amino-2-(4-nitrophenyl)propanamide (**4a**) were prepared from the corresponding ketones by the modified Strecker synthesis[3]. The obtained 2-aminoalkanenitriles were hydrolyzed in the medium of hydrogen peroxide or sulfuric acid to give the respective 2-aminoalkanamides, which were acylated[3] with 4-nitrobenzoyl chloride in anhydrous chloroform except for compound **4a**. The carboxamides 4-nitrobenzamide (**3a**), *N*-methyl-4-nitrobenzamide (**3b**), and *N*-(2-methylpropyl)-4-nitrobenzamide (**3c**) were prepared from 4-nitrobenzoyl chloride and the corresponding amine in anhydrous chloroform using triethylamine as a base. The identity of compounds **1b–1d**, **2b** and **2c** was verified by the ^{1}H NMR spectra which are presented in Table I. The results of elemental analyses, melting points and yields are given in Table II.

TABLE I

^{1}H NMR spectra of *N*-[2-(4-nitrobenzoylamino)alkanoyl]pyrrolidines **1b–1d** and substituted 2-(4-nitrobenzoylamino)alkanamides **2b** and **2c**

Compound	NH (d)	NHC**H**R (m)	NHCHC**H**$_3$ (d)	C**H**$(CH_3)_2$ (m)	CH$(CH_3)_2$ (2 × d)	NCH_2 (m)	CH_2 (m)	$CONH_2$ (2 × s)	Arom. H AA′XX′
1b[a]	7.52 ^3J = 6.3	4.88	1.45 ^3J = 6.8	–	–	3.50, 3.67 2 × m	1.92, 2.0 2 × m	–	7.79 (2 H) 8.26 (2 H)
1c[b]	–[c]	4.12	–	2.23	0.93, 0.95 ^3J = 6.9	3.09	1.83	–	8.11 (2 H) 8.34 (2 H)
1d[b]	8.87[d]	–	1.52[e] (6 H)	–	–	3.13	1.86	–	8.02 (2 H) 8.35 (2 H)
2b[b]	8.88 ^3J = 7.5	4.46	1.39 ^3J = 7.2	–	–	–	–	7.08, 7.51	8.17 (2 H) 8.36 (2 H)
2c[b]	8.64 ^3J = 8.7	4.33[f] ^3J = 8.7	–	2.18	0.97, 0.99 ^3J = 6.7	–	–	7.16, 7.58	8.16 (2 H) 8.36 (2 H)

[a] $CDCl_3$. [b] $(CD_3)_2SO$. [c] The signal was not detected. [d] Singlet. [e] $NHC(CH_3)_2$ system, singlet. [f] Triplet.

TABLE II
Melting points, yields of syntheses, and elemental analyses of *N*-acids **1a–1d**, **2a–2h**, **3a–3c**, and **4a**

Compound	M.p., °C (ref.)	Yield %	Formula (M.w.)	Solvent	Calculated/Found		
					% C	% N	% H
1a	171–175	52	$C_{13}H_{15}N_3O_4$	$CHCl_3$–C_6H_{12}	–	–	–
	(171–175)[a]		(277.3)	(3 : 1)	–	–	–
1b	180–182	68	$C_{14}H_{17}N_3O_4$	$CHCl_3$–C_6H_{12}	57.72	5.88	14.42
	–		(291.3)	(2 : 1)	57.72	5.92	14.36
1c	152–154	70	$C_{16}H_{21}N_3O_4$	$CHCl_3$–C_6H_6	60.17	6.62	13.16
	–		(319.4)	(1 : 1)	59.66	6.49	12.90
1d	154–156	35	$C_{15}H_{19}N_3O_4$	$CHCl_3$–C_6H_{12}	59.00	6.27	13.76
	–		(305.3)	(3 : 1)	58.79	6.25	13.30
2a	244–246	67	$C_9H_9N_3O_4$	$CHCl_3$–C_6H_{12}	–	–	–
	(244–246)[b]		(223.2)	(1 : 1)	–	–	–
2b	237–238	66	$C_{10}H_{11}N_3O_4$	$CHCl_3$–CH_3OH	50.63	4.67	17.71
	–		(237.2)	(1 : 1)	50.86	4.80	17.56
2c	202–204	67	$C_{12}H_{15}N_3O_4$	$CHCl_3$–C_6H_{12}	54.33	5.70	15.84
	–		(265.3)	(3 : 1)	54.72	5.66	14.14
2d	229–232	72	$C_{11}H_{13}N_3O_4$	$CHCl_3$–C_6H_{12}	–	–	–
	(229–232)[c]		(251.2)	(2 : 1)	–	–	–
2e	181–183	81	$C_{13}H_{17}N_3O_4$	$CHCl_3$–C_6H_{12}	–	–	–
	(181–183)[c]		(279.3)	(1 : 1)	–	–	–
2f	201–202	70	$C_{14}H_{17}N_3O_4$	$CHCl_3$–C_6H_{12}	–	–	–
	(201–202)[c]		(291.3)	(1 : 1)	–	–	–
2g	125–128	79	$C_{16}H_{15}N_3O_4$	$CHCl_3$–CH_3OH	–	–	–
	(125–128)[c]		(313.3)	(1 : 1)	–	–	–
2h	198–201	90	$C_{16}H_{14}N_4O_6$	$CHCl_3$–CH_3OH	–	–	–
	(198–201)[c]		(251.2)	(1 : 1)	–	–	–
3a	197–199	85	$C_7H_6N_2O_3$	H_2O	–	–	–
	(199–200)[d]		(166.1)		–	–	–
3b	220–221	80	$C_8H_8N_2O_3$	H_2O	–	–	–
	(220)[b]		(180.2)		–	–	–
3c	117–118	78	$C_{11}H_{14}N_2O_3$	H_2O	–	–	–
	(117–118)[b]		(222.2)		–	–	–
4a	111–112	53	$C_9H_{11}N_3O_3$	$CHCl_3$–C_6H_{12}	–	–	–
	(111–112)[c]		(209.2)	(1 : 1)	–	–	–

[a] Ref.[17]. [b] Ref.[18]. [c] Ref.[3]. [d] Ref.[19]. [e] Ref.[20]. [f] Ref.[21].

Dissociation Constants

Spectrophotometry in 60 and 80% v/v DMSO was used to determine the dissociation constants of *N*-acids **1a–1d**, **2a–2h**, **3a–3c**, and **4a**: a 1 cm closeable quartz cell placed in thermostated cell compartment of spectrophotometer was charged with 2 ml of respective sodium methoxide solution, and 20 μl methanolic solution of substrate (c $1 . 10^{-2}$ mol l^{-1}) was injected thereto; the solution was mixed and its spectrum was measured within 5 s.

RESULTS AND DISCUSSION

When measuring the electron spectra of *N*-acids **1a–1d**, **2a–2h**, **3a–3c**, and **4a** in a series of sodium methoxide solutions in MeOH–DMSO, we obtained records with well-developed isosbestic points. *N*-Acids **1b** (60% v/v DMSO), **2b** (80% v/v DMSO), and **2c** and **2d** (60 and 80% v/v DMSO) showed a second isosbestic point in the most concentrated sodium methoxide solutions. For these substances the analytical wavelength was chosen just in this newly formed isosbestic point in order to ensure the constant value of absorbance of the conjugated base of indicator. The values of dissociation constants pK_A (where $pK_A = -pK_{exp}$) were read from the dependence of log I on log c_{MeO^-}, or from the dependence of log Q (log I – log c_{MeO^-}) on c_{MeO^-} if the base concentration was above 0.1 mol l^{-1}. In these cases the activity coefficients of the individual species are not equal to one, hence the dissociation constants were read from the straight-line dependence of log Q on c_{MeO^-}. The intercept at the axis of ordinates represented the value of dissociation constant extrapolated to infinitely diluted solution of sodium methoxide[4] (Table III).

The changes in composition of MeOH–DMSO binary mixtures considerably affected the values of dissociation constants of *N*-acids. Increasing content of polar aprotic DMSO (which solvates anions less efficiently) in the mixture shifted the reaction of *N*-acid with methoxide ion in the direction of lower solvation requirements, *i.e.* in the direction of *N*-anion[5], which resulted in an acidity increase of all the *N*-acids measured when going from 60 to 80% v/v DMSO (Table III). On the other hand, sodium methoxide is considerably solvated in methanol, hence the sodium cation itself is less accessible to formation of ion pairs with *N*-anions. Increasing DMSO content decreases solvation of methoxide, which makes the formation of ion pairs more likely. The stabilization of *N*-anions by ion pairs results in increased acidity of the *N*-acids measured. The formation of the new isosbestic point in the case of the *N*-acid containing a single centre of dissociation (compound **1b** in 60% v/v DMSO) could be interpreted by formation of ion pairs, but we rejected this interpretation on the basis of the following experiment: into each methoxide solution used such an amount of 18-crown-6-ether was added that all the sodium ions present were transformed into the complex. From the records it is obvious, that the new isosbestic point is formed even at these conditions. The existence of the new point must only be due to formation of some other entity in

the most concentrated solutions of methoxide, the structure of which could not be elucidated.

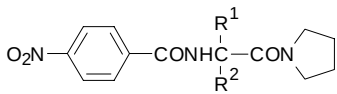
Our discussion will start from pyrrolidine derivatives **1a–1d**, where the dissociation centre is unambiguous and, at the same time, these substances bear the closest resemblance to the intermediates of the cyclization reaction studied.

Carboxamide group has practically identical electron-acceptor properties as carboxypyrrolidide group, which follows from the values σ_I (refs[6,7]) ($\sigma_I(CONH_2)$ = 0.28 and $\sigma_I(CON(CH_3)_2)$ = 0.28, the value found for a group most similar to $CON(CH_2)_4$). On the other hand, there is a considerable difference in the size of the two groups and, moreover, carboxamide group contains relatively acidic hydrogen atoms. The effect of replacement of carboxamide group by carboxypyrrolidide group can be documented on the values of dissociation constants of *N*-acids **1a** and **2a** (Table III). *N*-Substituted pyrrolidine **1a** is a weaker acid by 0.3 and 0.8 orders of magnitude in 60 and 80% v/v DMSO, respectively, as compared with 2-(4-nitrobenzoylamino)alkanamide **2a**. The

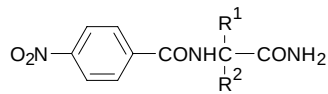
TABLE III
pK_A values of *N*-acids **1a–1d, 2a–2h**, **3a–3c**, and **4a** and values of their absorption maxima (λ_{max}, nm) in 60 and 80% v/v DMSO

N-Acid	pK_A		λ_{max}	
	60% v/v DMSO	80% v/v DMSO	60% v/v DMSO	60% v/v DMSO
1a	–0.52	–1.23	268	271
1b	0.06	–1.22	269	270
1c	2.04	1.12	268	266
1d	2.38	2.05	268	267
2a	–0.83	–2.00	268	269
2b	–0.70	–1.73	274	275
2c	–0.21	–1.29	268	268
2d	0.27	–1.12	268	269
2e	0.42	–1.00	271	270
2f	–	–0.90	–	275
2g	–0.60	–1.94	267	269
2h	–1.92	–3.05	276	272
3a	0.40	–0.53	264	265
3b	0.75	–0.47	267	268
3c	1.35	0.02	268	268
4a	1.25	–	282	–

acidity of *N*-acid **1a** is lowered by steric hindrance to solvation[8,9] of benzamide centre due to the distant bulky $CON(CH_2)_4$ group. Introduction of methyl (**1b**) or isopropyl (**1c**) substituent on the acetamide α-carbon atom in *N*-substituted pyrrolidines brings about a drop in acidity by 0.45 or 2.5 (in 60% v/v DMSO) and by 0.0 or 2.4 (in 80% v/v DMSO) orders of magnitude, respectively, as compared with *N*-acid **1a**. Introduction of two methyl groups to the same centre (**1d**) causes another acidity drop, namely by 2.9 and 3.3 orders of magnitude in 60 and 80% v/v DMSO, respectively, as compared with *N*-acid **1a**. The magnitude of alkyl substituents at α-carbon atom of acetamide in *N*-acids **1b–1d**, together with the bulky carboxypyrrolidide group, distinctly affect the extent of steric hindrance to solvation of *N*-anions and, hence, their acidities. The series was not extended by further *N*-acids with still bulkier alkyl or aryl substituents on the acetamide α-carbon atom because of their too low acidity in the medium used.

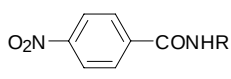


1

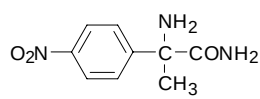


2

1, **2**	**a**	**b**	**c**	**d**	**e**	**f**	**g**	**h**
R^1	H	H	H	CH_3	CH_3	$-(CH_2)_5-$	CH_3	CH_3
R^2	H	CH_3	i-C_3H_7	CH_3	i-C_3H_7		C_6H_5	4-NO_2-C_6H_4



3	
a	H
b	CH_3
c	i-C_4H_9



4

The values of dissociation constants of pyrrolidine derivatives **1b–1d** were confronted with pK_A of 2-(4-nitrobenzoylamino)alkanamides **2a–2d** bearing the same substituents on the acetamide α-carbon atom. From the dissociation constant values (Table III) it is obvious that the steric hindrance to solvation of benzamide centre is practically insignificant, the acidity drop of *N*-acids **2a–2d** being predominantly due to the electron saturation of this centre by adjacent electron-donor alkyl groups.

A suitable model for quantification of the extent of inductive effect of alkyl substituent was found in *N*-alkyl substituted 4-nitrobenzamides **3a–3c** whose acidity decreases proportionately to the substituent inductive effect; this corresponds with the

conclusion[10] made from measurements of a more extensive series of *N*-acids (*N*-alkyl and aryl substituted benzenesulfonamides). Therefore, the series of *N*-alkyl substituted 4-nitrobenzamides was not extended by other *N*-acids.

Let us now deal with the question of the hydrogen atom which is split off from the molecules of the *N*-acids **2a–2h** studied. With regard to the experiments carried out by Bordwell[11,12] and other authors[13,14] (pK_A of acetamide and benzamide in DMSO is 25.5 and 23.35, respectively), we presumed from the beginning that the hydrogen atom in question came from benzamide group. This can now be supported by the following arguments: the absorption maxima of *N*-acids **2a–2h** are within a narrow interval (267–276 nm, see Table III), which can be interpreted as a change in the same chromophore (4-nitrobenzamide itself has λ_{max} = 275 nm in ethanol[15,16]), and none of *N*-acids **2a–2c** undergoes the cyclization reaction (the corresponding derivative of imidazolinone was not prepared) because the ionisation takes place at the benzamide centre. *N*-Acids **2d–2h** give the respective cyclization products, which means that the ionisation at acetamide centre is possible, but the values of dissociation constants can hardly tell us anything about the ability of the substrate to cyclize. From the values of dissociation constants of amides **2d–2h** it is also impossible to estimate the amounts of benzamide anion and particularly of the reactive acetamide anion or their proportions in the reaction mixture. A possibility leading to an approximate comparison of acidities of the two centres was offered by measurements of dissociation constants of 2-aminoalkanamide **4a**, which can only undergo dissociation at its acetamide centre. A comparison of acidities of both centres was only possible with the pair of model substances **4a** (pK_A of acetamide centre) and **2h** (pK_A of benzamide centre): compound **4a** showed "a measurable acidity" as an *N*-acid in the medium studied (making a quite acceptable presumtion that the replacement of amine hydrogen by 4-nitrophenyl group in indicator **4a** did not markedly affect the acidity of acetamide centre in compound **2h**). The values of dissociation constants of 2-aminoalkanamide **4a** (60% v/v DMSO) and its *N*-(4-nitrobenzoyl) derivative **2h** (Table III) show that the acetamide centre is at least 3 orders weaker acid than the benzamide centre. From this finding it follows that in the cyclization reaction of substituted 2-(4-nitrobenzoylamino)alkanamide in MeOH–DMSO solution of sodium methoxide the concentration ratio of reactive acetamide anion to benzamide anion present in the rapid pre-equilibrium is about 1 : 1 000. The low concentration of acetamide anion is compensated by its considerable reactivity in the subsequent cyclization reaction.

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