DISSOCIATION OF AMIDES IN STRONGLY BASIC MEDIUM OF SODIUM METHOXIDE IN DIMETHYL SULFOXIDE–METHANOL MIXTURES

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The dissociation constants of eleven amides have been measured in methanol and its mixtures with dimethyl sulfoxide (10 to 80% v/v) using sodium methoxide as the base. The experimental dissociation constants have been used to construct the H_- acidity function as a function of methoxide concentration and composition of the DMSO–MeOH mixture as well as function of methoxide concentration in methanol. Moreover, with the help of construction of acidity function, the functions have been devised for constant sodium methoxide concentrations (0.025, 0.1, and 0.2 mol l^{-1}) and changing composition of the DMSO–MeOH mixture.
Key words: Acidity functions; Dissociation constants of amides.

The sodium methoxide catalyzed cyclization of *N*-substituted α-aminoamides **1a**–**1d** represents one of alternative syntheses of substituted imidazolinones, one of the new promising classes of herbicides[1]. Other conceivable synthetic routes to these compounds involve reactions of imidoesters with esters of amino acids[2], oxidations of imidazoles with lead(IV) acetate[3], desulfurization of thiohydantoins with Raney nickel[4], and cyclizations of aminoamides in strongly basic media (barium hydroxide in methanol[5], sodium hydride in toluene[6], or sodium methoxide in methanol[6]). The quoted papers dealing with the cyclization reactions of aminoamides are predominantly focused on synthetic aspects. The authors did not pay attention to systematic kinetic studies, measurements of dissociation constants of the *N*-substituted α-aminoamides, and a choice of suitable solvent systems.

On the basis of the papers mentioned we can suggest a reaction mechanism for the cyclization reactions of *N*-substituted α-aminoamides catalyzed with sodium methoxide (Scheme 1). The cyclization itself is probably initiated by a rapid pre-equilibrium of deprotonation of the substrate at one of its acidic centres, only anion **3** formed by deprotonation at the acetamide centre being able to undergo the next cyclization steps.

Any detailed kinetic study of the given cyclization reaction needs the knowledge of actual concentration of anion **3**, which can be determined from the dissociation constants and acidity functions. Suitable media involve protic solvents or their mixtures

with polar aprotic solvents, which readily dissolve the reactants and do not much solvate the base used.

The acid-base properties of weak acids in protic and aprotic solvents in the presence of sodium methoxide as the base have already been dealt with by some authors using various series of substituted C-, N-, and O-acids. For instance, Schall and Lambert[7] as well as More O'Ferrall and Ridd[8] used series of substituted anilines and diphenylamines as the indicators for the $MeO^-/MeOH$ system. The H_- and H_m scales obtained by them, of course, depend on the type of the indicator used: the two scales are practically identical for the same value of autoprotolytic constant of methanol. Kaválek[9] constructed an acidity function in the same medium, using a series of substituted formanilides. Rochester[10] describes the same medium by several scales using several series of substituted phenols. His acidity scales for O-acids differ slightly from one another, but they show a considerable deviation from the H_m and H_- scales found with the help of series of substituted N-acids.

Bowden and Stewart[11] and Kroeger and Stewart[12] constructed a H_- scale with series of C-acids (substituted α-cyanostilbenes) for the binary solvent system dimethyl sulfoxide–methanol (DMSO–MeOH), which represents a transition between a protic and an aprotic solvent. This solvent system also seems to be the most suitable for syntheses of imidazolinone derivatives as well as for mechanistic studies of the cyclization reaction of N-substituted α-aminoamides. There is no available paper dealing with the acid-base properties of N-substituted α-aminoamides **1a**, **1b**, **1d**, **1e**, and **1k** in the DMSO–MeOH medium with sodium methoxide as the base.
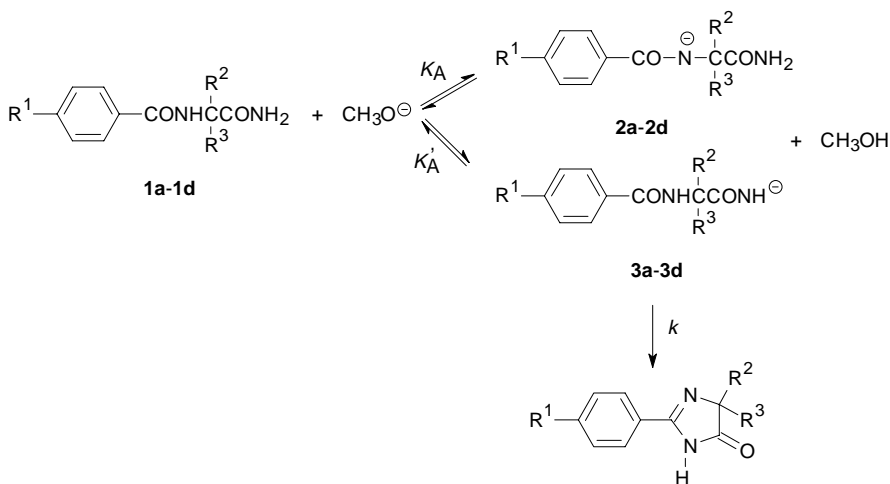
SCHEME 1

The papers quoted present the acidity functions constructed with the help of substituted anilines and phenols for various concentrations of sodium methoxide and constant composition of the solvent mixture, or for one concentration of sodium methoxide and changing composition of the mixed solvent. (The effect of both factors, *i.e.* the base concentration and solvent composition, has not been studied, nor have been constructed acidity functions for individual DMSO–MeOH mixtures.)

The aim of the present communication, therefore, is a study of the acid-base properties of *N*-substituted α-aminoamides in DMSO–MeOH mixtures with sodium methoxide as the base. For the purpose of construction of acidity function the series of *N*-substituted α-aminoamides has been extended by substituted acetanilides and formanilides, which has made it possible to cover the whole concentration range of sodium methoxide in the DMSO–MeOH mixture.

THEORETICAL

The deprotonation of acid HA in solutions of sodium methoxide in DMSO–MeOH according to Eq. (*1*) can be described by the thermodynamic equilibrium constant K_A expressed by Eq. (*2*).

$$HA + MeO^- \;\; \rightleftharpoons \;\; A^- + MeOH \tag{1}$$

$$K_A = ([A^-]a_{MeOH}/[MeO^-][HA])(\gamma_{A^-}/\gamma_{MeO^-}\,\gamma_{HA}) \tag{2}$$

The standard modification of Eq. (*2*) gives Eq. (*3*) wherefrom the acidity function H_- can be defined as in Eq. (*4*).

$$pK_A = \log I + \log [MeO^-] + \log (\gamma_{MeO^-}\,\gamma_{HA}/\gamma_{A^-}) - \log a_{MeOH} \tag{3}$$

$$H_- = \log [MeO^-] + \log (\gamma_{MeO^-}\,\gamma_{HA}/\gamma_{A^-}) - \log a_{MeOH} \tag{4}$$

In Eq. (*2*) the activities are defined by a product of concentration and activity coefficient. With changing sodium methoxide concentration or changing methanol content in its mixture with dimethyl sulfoxide the activity coefficients need not necessarily remain equal to one. That is why we must know their changes affected by the two factors.

The dissociation constants of indicators can be calculated from Eq. (*3*) on the condition that the activity coefficients are equal to one. If not, then the dissociation constants

can be obtained from the linear dependence $\log Q = \log I + \log [\text{MeO}^-]$ *vs* c_{MeO^-} as the intercept at ordinate axis[8]. The obtained value of $\log Q_0$ is an extrapolation to the infinitely diluted solution of methoxide.

An alternative possibility of evaluation of dissociation constants is based on the application of the general acidity function[13] published in the form of Eq. (5) for methanolic solutions of sodium methoxide,

$$\log I + \log [\text{MeO}^-] = \text{p}K_A + m^* X , \qquad (5)$$

where X is a function of analytical concentration of sodium methoxide describing the nonideality of medium, and m^* is a sensitivity coefficient.

EXPERIMENTAL

Syntheses of the Substances Studied

The indicators 2-(4-nitrobenzoylamino)-2,3-dimethylbutanamide (**1a**), 2-(4-nitrobenzoylamino)-2-phenylpropanamide (**1b**), 2-(4-nitrobenzoylamino)-2(4-nitrophenyl)propanamide (**1c**), 2-(4-nitrobenzoylamino)-2,3-dimethylbutanenitrile (**1d**), and 4-nitrobenzoylglycinamide (**1e**) were prepared by known methods[14]. The acetanilides 4-nitroacetanilide (**1f**) and 3-nitroacetanilide (**1g**) were prepared by acetylating the respective amines with acetic anhydride; the formanilides 4-nitroformanilide (**1h**), 3-nitroformanilide (**1i**), and 4-bromoformanilide (**1j**) were prepared by formylating the respective amines with 98% formic acid[15].

Synthesis of *N*-(4-Nitrobenzoylaminoethanoyl)pyrrolidine (**1k**)

Glycine (20 g, 0.26 mol) was dissolved in methanol (150 ml), the cold solution was saturated with hydrogen chloride (37 g, 1 mol), and then refluxed 4 h. After distilling off the methanol, quantitative yield (33.7 g) of methyl glycinate hydrochloride was isolated; m.p. 172–175 °C (ref.[16] gives m.p. 172–174 °C).

Methyl glycinate hydrochloride (2 g, 0.016 mol) was mixed with chloroform (35 ml) and triethylamine (4.45 ml, 0.032 mol) and treated with 4-nitrobenzoyl chloride (2.97 g, 0.016 mol) in chloroform (10 ml). The temperature of reaction mixture increased to 50 °C, and after standing for 24 h a homogeneous solution was formed which was evaporated until dry. The yellowish crystals were washed with water (2 × 5 ml) and recrystallized from distilled water to give 2.46 g (65%) methyl 4-nitrobenzoylglycinate, m.p. 150–152 °C (ref.[17] gives m.p. 151–152 °C). For $C_{10}H_{10}N_2O_5$ (238.2) calculated: 50.42% C, 4.23% H, 11.76% N; found: 50.31% C, 4.21% H, 11.59% N.

A suspension of methyl 4-nitrobenzoylglycinate (1 g, 4.2 mmol) in pyrrolidine (7.1 g, 8.33 ml, 0.1 mol) was refluxed until a dark yellow homogeneous solution was formed (6 h). Then the excess pyrrolidine was distilled off in vacuum, and the distillation residue was recrystallized from a chloroform–cyclohexane mixture (1 : 1). The acylated pyrrolidine **1k** (0.61 g, 52%) melted at 174–178 °C (ref.[18] gives m.p. 174–177 °C). For $C_{13}H_{15}N_3O_4$ (277.3) calculated: 56.31% C, 5.45% H, 15.15% N; found: 56.07% C, 5.44% H, 15.10% N. The identity of product was verified by the ^{1}H NMR spectrum (AMX 360 Bruker spectrometer; 360.14 MHz; 25 °C). The chemical shifts are referenced to the solvent

signal (δ(^{1}H) 7.25): 8.25 and 7.79 AA′XX′, 2×2 H (arom.); 7.52 brs, 1 H (NH); 4.15 d, $^3J = 4.03$ (NHCH$_2$); 3.52 t and 3.43 t, 2×2 H ($2 \times$ NCH$_2$); 2.02 m and 1.90 m, 2×2 H ($2 \times$ CH$_2$).

Solvents

Methanol p.a. (Aldrich) was distilled 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 mol l^{-1} solution by dissolving sodium metal in methanol rid of carbon dioxide by distillation under argon. Solutions of required concentrations were obtained by diluting this stock solution with methanol, and the sodium methoxide content was determined by titration with standard hydrochloric acid solution.

Measurements of Dissociation Constants

The dissociation constants of indicators **1a**–**1k** were measured spectrophotometrically in DMSO–MeOH mixtures, containing from 0 to 80% v/v dimethyl sulfoxide, at 25 °C using the diode array apparatuses Hewlett-Packard 8452 and 8453. A 1 cm quartz cell with a lid was charged with 2 ml respective sodium methoxide solution and placed in the thermostated cell compartment of the spectrophotometer. Then 20 µl methanolic solution of substrate (c 1 . 10^{-2} mol l^{-1}) was injected and after mixing the spectrum was measured to 5 s in the wavelength range from 200 to 500 nm.

RESULTS AND DISCUSSION

The indicators **1a**–**1k** used in the construction of the acidity function gave spectral records with sharp and well-developed isosbestic points. The spectrum of the conjugate base of *N*-substituted α-aminoamide **1e** exhibited a second isosbestic point due to the change of methoxide concentration, which we interpret by simultaneous dissociation at the benzamide and acetamide centres (Scheme 1). Therefore, the analytical wavelength was chosen just at this newly formed isosbestic point to ensure a constant value of absorbance for the conjugate base. Acetamide is a *ca* two orders weaker *N*-acid than benzamide[19] (pK_A's of benzamide and acetamide in DMSO are 23.35 and 25.5, respectively), hence in a molecule of *N*-substituted α-aminoamides **1a**, **1b**, **1d**, and **1e** the dissociation will preferably take place at the benzamide centre unless the α-carbon in the acetamide moiety is substituted (R$_{2,3}$ = H). If it is substituted, then the dissociation at this centre is sterically hindered (R$_{2,3} \neq$ H), and the acetamide centre is also partially deprotonated[20]. This conclusion is also supported by the UV-VIS spectra of *N*-substituted α-aminoamides **1a**, **1b**, and **1d** which show no second isosbestic points in the case of disubstitution (R$_{2,3} \neq$ H). For verification of this conclusion we measured, too, the spectra of 4-nitrobenzoylglycinamide (**1e**) where it is also possible to deprotonate two centres and no steric hindrance is present. The UV-VIS spectra measured revealed that the dissociation took place at the benzamide centre, but in the most concentrated solutions of sodium methoxide the acetamide centre was simultaneously deprotonated, which was manifested by appearance of a new isosbestic point. Another interpretation of the new isosbestic point can lie in the change of optical density when the spectra of the conjugate base are measured, especially so if a nitro group is present as the 4-sub-

stituent, which results in considerable delocalization of negative charge of the conjugate base, or in a specific effect of mixed solvent on the deprotonation of substrate which is noticeable just in the methoxide solutions of the highest concentrations.

Also when measuring the spectra of conjugate bases of some acetanilides and formanilides, we have observed shifts in the existing isosbestic points and formation of new ones. In particular, such changes were observed with the indicators **1f–1i** in neat methanol and in its mixtures with 10 and 20% v/v DMSO. These spectra were statistically analyzed with the help of the method of principal components[21]. The absorbance values were arranged into a source matrix whose columns and rows corresponded to selected wavelengths and to the individual methoxide concentrations, respectively. By decomposition of this matrix we obtained the first principal component with the help of which it is possible (in the so-called short cycle) to reconstruct the original matrix without disturbing effects. For instance, the application of this procedure to the spectral record of indicator **1f** in 20% v/v DMSO (Fig. 1) gave the result depicted in Fig. 2.

The values of analytical wavelengths and ΔpK_A (read from the dependence of log I vs log c_{MeO^-} or log Q vs c_{MeO^-} and referenced to the standard indicator **1h** in methanol) are given in Table I, and the limit values of log I vs c_{MeO^-} in Table II. The results were treated in two ways: with the help of general acidity function[13] and by constructing the acidity function with the help of the recently suggested algorithm[22].

Calculation of ΔpK_A of Studied Indicators in Methanol Using General Acidity Function[13]

The differences of dissociation constants of the indicators **1c**, **1d**, and **1g–1j** in methanol were calculated by means of the general acidity function. The sensitivity coefficients m^* were calculated from the dependences of log Q_{st} vs log Q, where log Q_{st} and log Q are the values for the standard indicator **1h** and those for the given indicator, respec-
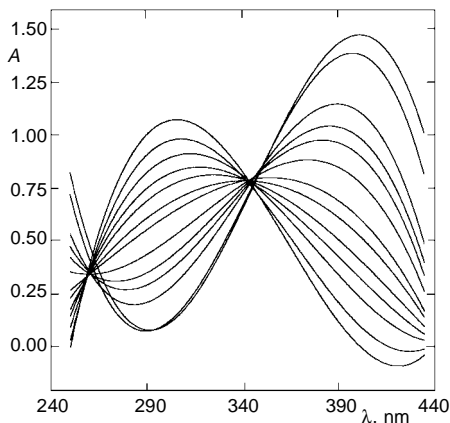

FIG. 1
Electronic spectra of 4-nitroacetanilide measured in 20% v/v DMSO

TABLE I
The values of dissociation constants ΔpK_A read from the dependences of $\log I$ vs $\log c_{MeO^-}$ or $\log Q$ vs c_{MeO^-} referenced to indicator **1h** in methanol whose pK_A value was referred to zero, ΔpK_A calculated by means of construction of acidity function (ref.[22]), ΔpK_A and m^* values calculated by means of general acidity function in methanol (ref.[13])

Indicator	DMSO % v/v	λ^a, nm	ΔpK_A	q^b	ΔpK_A (ref.[22])	s^c	ρ^c	v^c	s_v^c	ΔpK_A (ref.[13])	m^*
1c	0	326	1.11	13	1.207	0.128	0.911	95.53	0.122	1.11 ± 0.02	0.57 ± 0.03
1d	0	318	0.65	10	0.639	0.093	0.863	98.08	0.065	0.56 ± 0.06	0.68 ± 0.06
1f	0	380	1.29	14	1.738	0.109	0.847	95.68	0.086		
1g	0	265	1.63	13	2.069	0.044	0.988	99.37	0.045	2.10 ± 0.15	0.73 ± 0.06
1h	0	364	0.00	12	0.000	0.084	1.040	98.30	0.084	0.06 ± 0.10	1.00 ± 0.01
1i	0	266	0.34	13	0.372	0.051	0.923	99.85	0.023	0.25 ± 0.12	0.41 ± 0.08
1j	0	273	1.25	15	1.351	0.114	0.945	96.49	0.113	1.34 ± 0.08	0.77 ± 0.05
1c	10	322	1.00	12	0.895	0.042	1.018	99.50	0.043		
1d	10	320	0.49	11	0.421	0.064	1.112	99.92	0.018		
1i	10	259	0.15	12	0.148	0.065	1.045	99.19	0.062		
1c	20	316	0.76	9	0.755	0.024	1.003	99.80	0.026		
1d	20	320	0.20	10	0.208	0.026	1.003	99.68	0.028		
1f	20	344	0.92	10	0.864	0.084	1.008	98.16	0.089		
1g	20	264	1.23	9	1.160	0.095	1.052	97.76	0.097		
1h	20	372	-0.45	10	-0.448	0.037	0.983	99.55	0.038		
1i	20	274	-0.03	13	0.039	0.108	0.870	99.69	0.039		
1j	20	271	0.84	11	0.911	0.101	0.945	98.44	0.097		
1c	30	350	0.49	9	0.486	0.042	0.957	99.37	0.040		
1d	30	330	-0.01	9	0.008	0.052	1.044	98.80	0.052		
1h	30	362	-0.67	10	-0.728	0.090	1.129	98.95	0.064		
1i	30	272	-0.27	11	-0.135	0.191	0.786	97.34	0.104		

TABLE I
(*Continued*)

Indicator	DMSO % v/v	λ^a, nm	ΔpK_A	q^b	ΔpK_A (ref.[22])	s^c	ρ^c	v^c	s_v^c	ΔpK_A (ref.[13])	m^*
1b	40	342	1.27	9	1.187	0.093	1.126	98.02	0.078		
1c	40	350	0.15	11	0.168	0.033	1.009	99.55	0.035		
1d	40	320	-0.39	10	-0.413	0.053	1.085	99.62	0.035		
1e	40	340	1.20	10	1.158	0.043	0.987	99.37	0.045		
1f	40	396	0.43	12	0.392	0.020	1.008	99.94	0.020		
1g	40	274	0.92	11	1.055	0.137	0.841	99.22	0.061		
1h	40	384	-1.07	11	-1.036	0.028	0.966	99.92	0.019		
1i	40	272	-0.65	10	-0.660	0.016	0.994	99.91	0.017		
1j	40	278	0.37	9	0.459	0.090	1.081	98.69	0.081		
1a	50	350	1.88	9	1.615	0.135	1.237	98.14	0.084		
1b	50	350	0.97	10	0.783	0.123	1.177	97.93	0.090		
1c	50	350	-0.20	11	-0.209	0.028	1.033	99.76	0.025		
1d	50	340	-0.77	10	-0.745	0.035	1.001	99.42	0.037		
1e	50	340	0.75	11	0.737	0.087	1.057	98.70	0.083		
1k	50	340	1.33	12	1.090	0.197	1.273	97.40	0.125		
1a	60	378	1.57	10	1.270	0.138	1.308	99.25	0.051		
1c	60	350	-0.77	9	-0.787	0.048	1.085	99.11	0.040		
1d	60	340	-1.25	9	-1.188	0.038	0.960	99.50	0.035		
1e	60	342	0.32	11	0.230	0.113	1.164	99.01	0.069		
1f	60	382	-0.55	10	-0.556	0.027	0.994	99.72	0.028		
1g	60	276	0.04	11	0.016	0.094	1.037	95.35	0.097		

TABLE I
(*Continued*)

Indicator	DMSO % v/v	λ^a, nm	ΔpK_A	q^b	ΔpK_A (ref.[22])	s^c	ρ^c	v^c	$s_v^{\,c}$	ΔpK_A (ref.[13])	m^*
1i	60	274	−1.55	9	−1.510	0.020	1.032	99.93	0.014		
1k	60	340	1.05	10	0.677	0.307	1.593	95.93	0.158		
1b	70	360	−0.15	9	−0.147	0.053	1.040	98.85	0.053		
1c	70	365	−1.42	9	−1.422	0.021	1.002	99.82	0.022		
1e	70	344	−0.25	11	−0.250	0.094	1.086	98.19	0.085		
1f	70	362	−1.23	11	−1.194	0.049	0.998	99.36	0.052		
1g	70	276	−0.86	11	−0.809	0.073	0.958	98.82	0.072		
1k	70	344	0.58	11	0.319	0.311	1.505	97.44	0.143		
1a	80	370	0.15	9	0.143	0.074	1.202	99.23	0.037		
1b	80	363	−0.79	12	−0.851	0.062	1.085	99.34	0.047		
1e	80	346	−0.85	9	−0.881	0.147	1.220	97.22	0.107		
1f	80	422	−2.02	7	−2.062	0.159	1.275	97.78	0.100		
1g	80	278	−1.39	10	−1.256	0.091	0.884	99.27	0.053		
1k	80	352	−0.08	11	−0.176	0.107	1.187	97.20	0.083		

[a] Values of analytical wavelengths (λ); [b] numbers of experimental points (q); [c] standard deviations (s) of ΔpK_A, slope of dependence of log I vs H_- (ρ), interpreted variability of slope (v) and its standard deviation (s_v) calculated by the published algorithm[22].

Table II

Values of limit ionization ratios $\log I$ vs c_{MeO^-} of indicators **1a**–**1k** in MeOH with 0–80% v/v DMSO

Indi-cator	DMSO % v/v	$\log I$		c_{MeO^-}, mol l^{-1}		Indi-cator	DMSO % v/v	$\log I$		c_{MeO^-}, mol l^{-1}	
		max	min	max	min			max	min	max	min
1c	0	0.70	−1.00	1.80	0.10	**1i**	40	0.83	−0.76	0.10	0.003
1d	0	0.65	−0.40	0.80	0.10	**1j**	40	0.71	−0.83	0.60	0.03
1f	0	0.38	−0.93	2.00	0.25	**1a**	50	0.42	−1.05	1.20	0.30
1g	0	1.08	−0.79	3.50	0.60	**1b**	50	0.88	−0.74	0.70	0.08
1h	0	1.02	−0.50	0.50	0.025	**1c**	50	0.71	−0.73	0.20	0.008
1i	0	1.02	−0.79	0.80	0.025	**1d**	50	0.52	−0.63	0.04	0.003
1j	0	0.72	−1.03	2.00	0.10	**1e**	50	0.91	−0.98	1.00	0.04
1c	10	0.77	−1.00	1.00	0.05	**1k**	50	0.73	−0.87	1.00	0.15
1d	10	0.73	−1.07	0.50	0.02	**1a**	60	0.57	−1.08	1.00	0.15
1i	10	0.90	−0.70	0.50	0.02	**1c**	60	0.74	−0.42	0.05	0.005
1c	20	0.69	−0.88	0.80	0.05	**1d**	60	0.70	−0.78	0.025	0.001
1d	20	0.41	−1.08	0.25	0.01	**1e**	60	0.57	−1.07	0.30	0.01
1f	20	0.90	−0.89	1.00	0.07	**1f**	60	0.39	−1.07	0.05	0.002
1g	20	0.80	−0.97	1.40	0.10	**1g**	60	0.74	−0.79	0.20	0.01
1h	20	1.00	−0.57	0.25	0.007	**1i**	60	1.06	−0.48	0.025	0.001
1i	20	0.95	−0.96	0.60	0.007	**1k**	60	0.81	−0.80	0.70	0.10
1j	20	0.89	−0.98	1.60	0.05	**1b**	70	0.68	−0.74	0.20	0.01
1c	30	0.42	−0.98	0.40	0.02	**1c**	70	0.97	−0.56	0.025	0.001
1d	30	0.45	−0.93	0.20	0.01	**1e**	70	0.96	−0.90	0.20	0.005
1h	30	0.92	−0.86	0.10	0.003	**1f**	70	1.05	−0.80	0.05	0.001
1i	30	0.91	−0.57	0.50	0.01	**1g**	70	1.05	−1.00	0.10	0.001
1b	40	0.58	−1.03	1.00	0.10	**1k**	70	1.01	−0.98	0.50	0.025
1c	40	0.72	−0.74	0.40	0.02	**1a**	80	0.48	−0.67	0.20	0.025
1d	40	0.95	−0.81	0.20	0.005	**1b**	80	1.07	−0.47	0.10	0.005
1e	40	0.65	−0.97	1.40	0.10	**1e**	80	0.68	−1.06	0.025	0.001
1f	40	0.66	−0.95	0.50	0.02	**1f**	80	1.31	−0.01	0.01	0.001
1g	40	0.83	−0.91	2.00	0.07	**1g**	80	1.00	−0.63	0.05	0.001
1h	40	1.15	−0.35	0.10	0.003	**1k**	80	0.67	−0.92	0.20	0.01

tively. The individual differences of dissociation constants were then calculated from Eq. (*5*) (Table I).

The calculated ΔpK_A values do not show any significant deviations from those obtained from the dependence of log *I* *vs* log c_{MeO^-} or log *Q* *vs* c_{MeO^-} (Table I) or the values of dissociation constants calculated by means of iterative construction of acidity function (Table I) even in spite of the fact that the requirement of constant ratio of activity coefficients of indicators and their respective conjugated bases was not fulfilled. From among the indicators measured, the acid-base properties of **1f** considerably deviated and this indicator was replaced by **1i** whose acid-base properties were the closest to the indicator series measured. The nonhomogeneity of ratios of activity coefficients of the series measured is predominantly caused by the application of several different structures of indicators, which made itself felt distinctly in the individual sensitivity coefficients *m**, as it can be seen in Table I. The structural variety, which is a considerable complication in constructing acidity functions, could not be avoided due to the absence of suitable indicators. It can be stated that the application of the constructed general acidity function to this series of *N*-acids leads (in spite of the abovementioned structural problem) to dissociation constants which agree well with the results obtained in the classic way or by the new iterative procedure of construction of acidity function.

Calculation of Dissociation Constants through Construction of Acidity Function

The acidity function H_- and the ΔpK_A values in individual DMSO–MeOH mixtures were calculated by means of the algorithm devised by Pytela[22]. 4-Nitroformanilide (**1h**) was used as the standard indicator, and to this value were referred the ΔpK_A's of the other indicators measured (Table I) and the calculated acidity functions in methanol
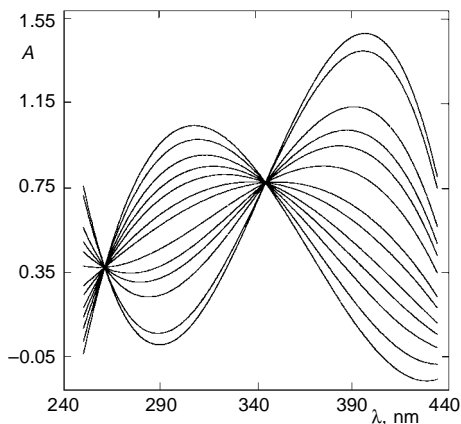

FIG. 2
Electronic spectra calculated by means of factor analysis from original data

and its mixtures with dimethyl sulfoxide (Table III) and H_- at constant concentrations of base and varying composition of the solvent mixture (Table III). In the way described we calculated, from the log I values measured, the ΔpK_A of indicators and their standard deviations and then the slope values of the dependence of log I vs H_-. One third of these calculated slope values exhibit statistically significant deviations from unit slope (from 0.786 to 1.593), which is especially the case with substituted acetanilides and formanilides **1f**–**1j** whose ratios of activity coefficients of indicator and its respective conjugate base are different from those of N-substituted α-aminoamides **1a**, **1b**, **1d**, **1e**, and **1k**. This deviation from unit slope is also observed with the indicator **1e** whose most concentrated solutions presented the above-mentioned problems potentially introducing error into the determination of log I. The ΔpK_A values calculated by this method (Table I) stand in very good accordance with the experimentally determined
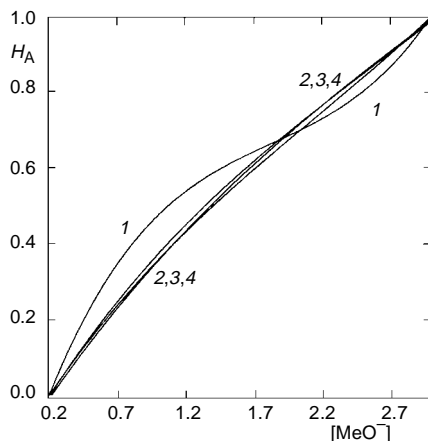

Fig. 3

The acidity function constructed with the help of algorithm[22] for changing concentration of sodium methoxide in methanol *2*, compared with published acidity functions for this medium *3* (ref.[9]), *4* (ref.[8]). The acidity function (curve *1*) constructed with the help of the same algorithm for changing sodium methoxide concentration in DMSO–MeOH mixture. The acidity functions H_- were standardized in the interval $\langle 0,1 \rangle$
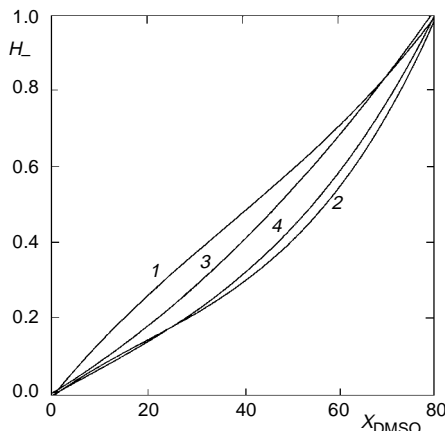

Fig. 4

Comparison of published[23] acidity function (curve *1*) with the acidity function constructed by means of algorithm[22] for constant sodium methoxide concentrations (0.025 mol l^{-1} (*2*), 0.1 mol l^{-1} (*3*), 0.2 mol l^{-1} (*4*)) and varying composition of DMSO–MeOH mixture. The acidity functions H_- were standardized in the interval $\langle 0,1 \rangle$

ΔpK_A values (Table I) as well as with those calculated by means of the general acidity function in methanol (Table I). The H_- acidity function has been constructed as a function of both variables, *i.e.* sodium methoxide concentration and solvent mixture composition, as well as a function of sodium methoxide concentration in methanol (Table III). For the individual DMSO–MeOH mixtures (from 10 to 80% v/v) we have constructed, using the algorithm, the acidity functions like those in methanol for changing base concentration, because standard indicators in the individual mixtures are not known. From among the series of indicators measured in the individual mixtures none could be considered standard since the calculated acidity functions in the individual mixtures cannot be mutually compared due to the fact that differences between the individual media measured are not known. The last type of the acidity functions constructed are those for constant methoxide concentrations (0.025, 0.1, 0.2 mol l^{-1}) and varying composition of DMSO–MeOH mixtures (Table III).

Analysis of Constructed and Published Acidity Functions in DMSO–MeOH Mixtures with Sodium Methoxide as Base

The acidity function constructed as a function of both variables, *i.e.* methoxide and DMSO concentration changes (Fig. 3, curve *1*), could not be compared with any similar published function, since no such function has been constructed yet. The acidity function devised as a dependence of methoxide concentration in methanol was compared with the functions published[8,9]. All the analyzed functions were standardized in the interval $\langle 0,1 \rangle$ (see Fig. 3, curves *2*, *3*, *4*), and it can be seen that the acidity function constructed by us is practically identical with those published. Another type of acidity functions constructed by us are those for varying composition of DMSO–MeOH mixture with constant concentration of the base. The acidity function of this type was only published[23] for the sodium methoxide concentration of 0.025 mol l^{-1}: it was standardized in the interval of $\langle 0,1 \rangle$ and compared with the acidity functions constructed by us for the sodium methoxide concentrations of 0.025, 0.1, and 0.2 mol l^{-1}. The constructed acidity functions differ from that published in the whole range (Fig. 4). The increasing concentration of polar aprotic DMSO affects the activity coefficients of the indicators used (amides *vs* amines) and their respective conjugated bases in different ways, which can be one of the reasons of differences between the functions compared. The experimental and calculated ΔpK_A values of indicators **1h**–**1j** in methanol were compared with the published values[9] and found identical with them within experimental error of determination of dissociation constants.

By constructing these acidity functions we managed to describe the DMSO–MeOH medium studied in the way sufficient for determination of actual concentration of the reactive anion (Scheme 1) formed in the pre-equilibrium of the cyclization reaction, and from this concentration to determine the real reaction rate of the cyclization reaction necessary for a detailed description of the reaction.

TABLE III
The H_- function calculated by means of construction of acidity function

[MeO$^-$] mol l^{-1}	$H_-{}^a$	$H_-{}^b$	DMSO % v/v	$H_-{}^c$	$H_-{}^d$	$H_-{}^e$
3.5	3.159	3.040	0	–1.563	–1.605	–2.525
3.0	2.681	2.569	10	–1.313	–1.409	–2.295
2.5	2.283	2.241	20	–1.078	–1.193	–2.126
2.0	2.029	1.936	30	–0.829	–0.952	–1.886
1.8	1.924	1.820	40	–0.594	–0.765	–1.561
1.6	1.845	1.726	50	–0.205	–0.557	–1.241
1.4	1.760	1.636	60	0.359	–0.042	–0.814
1.3	1.712	1.581	70	0.778	0.383	–0.239
1.2	1.692	1.528	80	1.739	0.529	0.395
1.0	1.575	1.415				
0.8	1.437	1.314				
0.7	1.350	1.209				
0.6	1.181	1.095				
0.5	1.038	0.985				
0.4	0.893	0.867				
0.3	0.718	0.705				
0.25	0.605	0.626				
0.2	0.507	0.529				
0.15	0.338	0.316				
0.1	0.162	0.196				
0.08	0.078					
0.07	–0.008	0.048				
0.05	–0.164	–0.132				
0.04	–0.252					
0.03	–0.386	–0.365				
0.025	–0.460	–0.454				

[a] For increasing concentrations of sodium methoxide and dimethyl sulfoxide; [b] for increasing concentration of sodium methoxide in neat methanol; [c] for constant concentration of sodium methoxide (0.025 mol l^{-1}) and increasing concentration of dimethyl sulfoxide; [d] for constant concentration of sodium methoxide (0.1 mol l^{-1}) and increasing concentration of dimethyl sulfoxide; [e] for constant concentration of sodium methoxide (0.2 mol l^{-1}) and increasing concentration of dimethyl sulfoxide.

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