Chemistry of Heterocyclic Compounds, Vol. 37, No. 5, 2001

SYNTHESIS AND PROPERTIES OF 1-ARYLSULFONYL-1,2,3-TRIAZOL-5-OLATES

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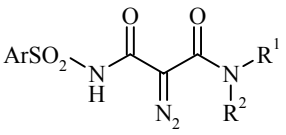
A series of 1-arylsulfonyl-4-carbamoyl-1,2,3-triazol-5-olates has been synthesized. The cyclization of diazoacetamides by the action of base has been shown to be reversible for the first time. 1-Arylsulfonyl-1,2,3-triazol-5-olates undergo rearrangement upon heating to give isomeric N-sulfonylcarbamoyldiazoacetimidolates. An equilibrium exists between these isomers in DMSO solution, which is shifted toward the acyclic derivative.

Keywords: diazomalonimidolates, ring–chain isomerization, diazo transfer reaction, thermodynamic stability.

The chemistry of aliphatic diazo compounds has been studied intensively during the past few decades [1-4]. Special interest among these compounds is found for diazoalkanes containing an α-carbamoyl group. These derivatives have been used to synthesize 1,2,3-triazoles and 1,2,3-thiadiazoles, which display antitumor, antiviral, and anti-inflammatory activity [5]. On the other hand, there have been no studies of the reactivity of N-sulfonyldiazoacetamides required for using these compounds in the synthesis of azoles [6].



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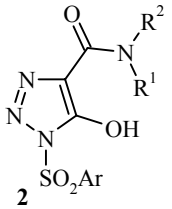

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We have already shown that the reaction of amides of malonic acid with benzenesulfonyldiazide in the presence of sodium ethylate leads to highly reactive and unstable diazoimidolates, which cyclize irreversibly to give 1,2,3-triazol-5-olates [7, 8]. We have also established that 5-hydroxy-1,2,3-triazoles obtained upon acidification, readily rearrange to give isomeric triazoles and diazo compounds.

In the present work, we synthesized N-sulfonyldiazomalondiamides **1** and studied the intramolecular cyclization to give sulfonyl derivatives of 1,2,3-triazoles **2**.

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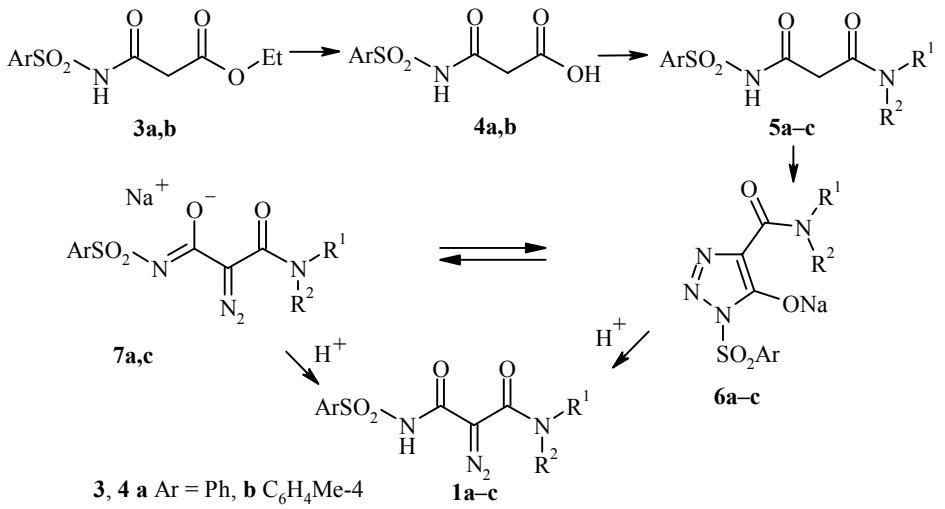


3, **4 a** Ar = Ph, **b** C_6H_4Me-4

1, 5	**a**	**b**	**c**	**6, 7**	**a**	**b**	**c**
Ar	C_6H_4Me-4	C_6H_4Me-4	Ph	Ar	C_6H_4Me-4	C_6H_4Me-4	Ph
R^1	$SO_2C_6H_4Me$-4	$C_6H_4NO_2$-4	C_6H_4 NO_2-4	R^1	$SO_2C_6H_4NO_2$-4	$C_6H_4NO_2$-4	C_6H_4 NO_2-4
R^2	H	Me	Me	R^2	Na	Me	Me

These compounds were obtained through the following scheme. The reaction of arylsulfonylamides with the acid chloride of the monoethyl ester of malonic acid gave esters of 2-(N-arylsulfonylcarbamoyl)acetic acid **3a,b**, which were hydrolyzed to give the corresponding acids **4a,b**. The reaction of these acids with amines in the presence of dicyclohexylcarbodiimide gave amides **5a-c**. The diazo transfer reaction [10] with **5a-c** gave sodium salts of triazoles **6a-c** in high yield. This reaction requires two equivalents of sodium ethylate and does not proceed with only one equivalent of base. The ^{1}H NMR spectrum of **6a** shows signals for the aromatic protons as doublets at 7.85, 7.70, 7.29, and 7.22 ppm and three-proton singlets at 2.36 and 2.32 ppm, which were assigned to the protons of the tosyl groups at $N_{(1)}$ of the triazole ring and in the carboxamide group, respectively. The treatment of an aqueous solution of triazole **6a** with 1 N hydrochloric acid gave a compound with two-proton doublets for aromatic protons at 7.71 and 7.22 ppm and a three-proton singlet at 2.32 ppm. The IR spectrum of this product, in contrast to the spectrum of **6a**, has a band at 2120 cm^{-1}, corresponding to diazo group stretching. Hence, this compound was identified as N,N'-disulfonyldiazomalondiamide **1a**.

These reactions proceed similarly for malondiamides **5b,c**, which have two substituents at the nitrogen atom of one of the amide functions. The ^{1}H NMR spectrum of 1-sulfonyltriazole **6b** shows a methyl group singlet at 2.36 ppm, while the corresponding signal for diazo compound **1b** is found at 2.34 ppm. The IR spectrum of **1b** has a diazo group stretching band at 2120 cm^{-1}.

In an attempt to recrystallize **6a-c** from carbon tetrachloride or ethanol, we isolated compounds with thin-layer chromatographic data different from the starting compounds. The IR spectra of these new compounds showed a diazo group stretching band at 2120 cm^{-1}. These data and the ^{1}H NMR spectra of these compounds (see Table 1) indicate that these compounds are diazo compounds **7a-c**.

Thus, we have shown that sodium 1-sulfonyl-1,2,3-triazol-5-olates **6a-c** may rearrange to open-chain isomers, diazoimidolates **7**. An equilibrium is established between the open-chain and ring forms for triazoles **6a-c** upon standing in DMSO-d_6 for 30 min with predominance of the open-chain isomers **7a-c** (see Table 2). Analogously, an equilibrium was established for solutions of **7a-c** in DMSO-d_6. The isomer ratio in both cases was the same within experimental error.

TABLE 1. ^{1}H NMR Spectra of Compounds Synthesized

Com-pound	Chemical shift and multiplicity of signals in the ^{1}H NMR spectra (DMSO-d_6), δ, ppm
5a	12.16 (2H, br. s, NH); 7.77 (4H, d, ArH); 7.41 (4H, d, ArH); 3.25 (2H, s, CH_2); 2.40 (6H, s, CH_3)
5b	12.6 (1H, br. s, NH); 9.12 (H, s, NH); 8.00 (2H, d, ArH); 7.56 (2H, d, ArH); 7.40 (2H, d, ArH); 7.20 (2H, d, ArH); 3.65 (2H, s, CH_2); 3.22 (3H, s, NCH_3); 2.32 (3H, s, $ArCH_3$)
5c	8.00 (2H, d, ArH); 7.58-7.65 (2H, m, Ph); 7.42 (2H, d, ArH); 7.30-7.40 (3H, m, Ph); 3.32 (2H, s, CH_2); 3.21 (3H, s, NCH_3)
6a	7.85 (2H, d, ArH); 7.70 (2H, d, ArH); 7.29 (2H, d, ArH); 7.22 (2H, d, ArH); 2.364 (3H, s, $ArCH_3$); 2.24 (3H, s, $ArCH_3$)
6b	8.08 (2H, d, ArH); 7.67 (2H, d, ArH); 7.53 (2H, d, ArH); 7.23 (2H, d, ArH); 3.22 (3H, s, NCH_3); 2.36 (3H, s, $ArCH_3$)
6c	8.08 (2H, d, ArH); 7.60-7.70 (2H, m, Ph); 7.54 (2H, d, ArH); 7.30-7.40 (3H, m, Ph); 3.215 (3H, s, NCH_3)
7a	7.70 (2H, d, ArH); 7.21 (2H, d, ArH); 2.316 (3H, s, $ArCH_3$)
7b	8.01 (2H, d, ArH); 7.60 (2H, d, ArH); 7.47 (2H, d, ArH); 7.20 (2H, d, ArH); 3.22 (3H, s, NCH_3); 2.33 (3H, s, $ArCH_3$)
7c	8.00 (2H, d, ArH); 7.58-7.65 (2H, m, Ph); 7.50 (2H, d, ArH); 7.30-7.40 (3H, m, Ph); 3.215 (3H, s, NCH_3)
9a	11.4 (2H, br. s, NH); 7.62 (4H, d, ArH); 7.12 (4H, d, ArH); 6.92 (1H, br. s, NH); 6.45 (1H, br. s, NH); 2.32 (6H, s, $ArCH_3$)
9b	11.8 (2H, br. s, NH); 8.00 (2H, d, ArH); 7.56 (2H, d, ArH); 7.45 (2H, d, ArH); 7.20 (2H, d, ArH); 6.90 (1H, br. s, NH); 5.88 (1H, br. s, NH); 3.22 (3H, s, NCH_3); 2.33 (3H, s, $ArCH_3$)
9c	12.1 (2H, br. s, NH); 8.00 (2H, d, ArH); 7.60-7.80 (2H, m, Ph); 7.50 (2H, d, ArH); 7.30-7.40 (3H, m, Ph); 6.44 (1H, br. s, NH); 6.05 (1H, br. s, NH), 3.25 (3H, s, NCH_3)
10a	7.75 (2H, d, ArH); 7.42 (2H, d, ArH); 3.14 (6H, s, 2 CH_3); 2.39 (6H, s, 2 CH_3)
10b	8.21 (2H, d, ArH); 7.76 (2H, d, ArH); 7.57 (2H, d, ArH); 7.42 (2H, d, ArH); 3.26 (3H, s, CH_3); 3.15 (3H, s, CH_3); 2.41 (3H, s, CH_3)
10c	8.22 (2H, d, ArH); 7.50-7.93 (7H, m, ArH); 3.26 (3H, s, CH_3); 3.19 (3H, s, CH_3)

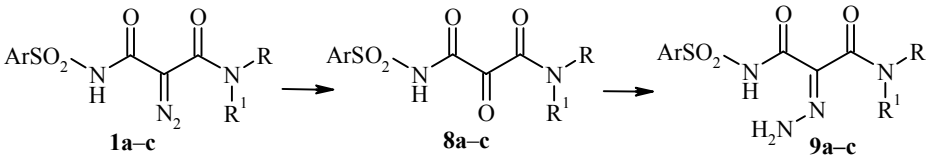
TABLE 2. Equilibrium Mixtures of Triazoles **6a-c** and Diazo Compounds **7a-c** Determined from the Integral Intensities in the ^{1}H NMR Spectra in DMSO-d_6

Compound	Content in mixture, %	
	6	**7**
a	15	85
b	5	95
c	6	94

The liberation of nitrogen was noted upon maintaining solutions of diazo compounds **1a-c** in DMSO-d_6 but the shape of the ^{1}H NMR spectrum did not change. The cyclization to 1-sulfonyl-1,2,3-triazole presumably does not occur in this case, but rather decomposition of the diazo compounds to corresponding ketones **8a-c**, which is similar to previously reported behavior [11, 12]. In order to check this hypothesis, solutions of diazo compounds **1a,b** in DMSO-d_6 were heated at 85°C and then treated with aqueous hydrazine hydrate. IR and ^{1}H NMR spectroscopy and elemental analysis indicated that the products isolated were hydrazones **9a**,**b**.

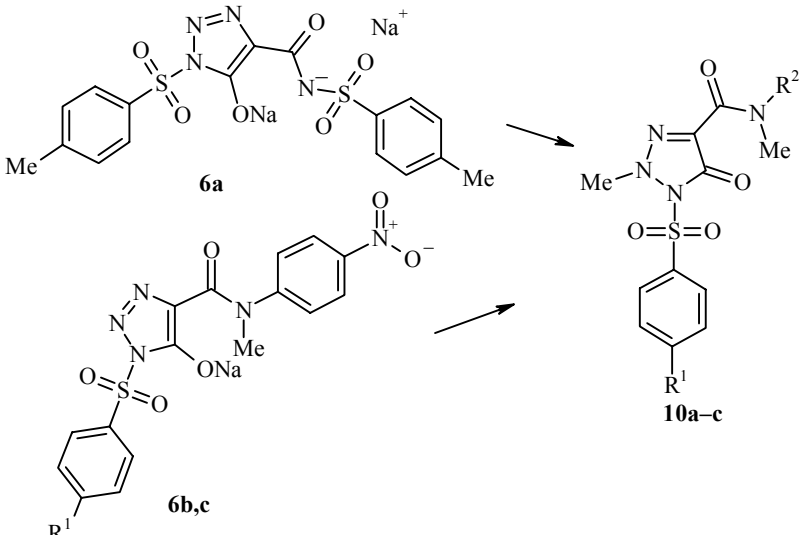
TABLE 3. Physicochemical Characteristics of Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %		mp, °C	Yield, %
		N	S		
1a	$C_{17}H_{16}N_4O_6S_2$	12.45 / 12.84	14.30 / 14.69	202-208	89
1b	$C_{17}H_{15}N_5O_6S$	16.50 / 16.78	7.32 / 7.68	186-189	92
1c	$C_{16}H_{13}N_5O_6S$	17.03 / 17.36	7.48 / 7.95	215-217	95
3a	$C_{11}H_{13}NO_5S$	5.69 / 5.16	12.12 / 11.82	83-85	70
3b	$C_{12}H_{15}NO_5S$	5.15 / 4.91	11.85 / 11.24	97-98	75
4a	$C_9H_9NO_5S$	6.10 / 5.76	12.97 / 13.18	138-139	75
4b	$C_{10}H_{11}NO_5S$	5.67 / 5.44	12.12 / 12.46	137-140	83
5a	$C_{17}H_{18}N_2O_6S_2$	6.92 / 6.82	15.42 / 15.62	136-140	70
5b	$C_{17}H_{17}N_3O_6S$	10.62 / 10.74	8.13 / 8.19	156-158	65
5c	$C_{16}H_{15}N_3O_6S$	11.35 / 11.13	8.47 / 8.50	140-141	63
6a	$C_{17}H_{14}N_4Na_2O_6S_2\cdot 2H_2O$	10.15 / 10.85	12.13 / 12.42	>250 dec.	63
6b	$C_{17}H_{14}N_5NaO_6S\cdot 2H_2O$	14.32 / 14.73	6.41 / 6.74	>250 dec.	68
6c	$C_{16}H_{12}N_5NaO_6S\cdot 2H_2O$	15.00 / 15.18	6.75 / 6.95	>250 dec.	62
7a	$C_{17}H_{14}N_4Na_2O_6S_2\cdot 2H_2O$	10.58 / 10.85	12.21 / 12.42	>250 dec.	81
7b	$C_{17}H_{14}N_5NaO_6S\cdot 2H_2O$	14.31 / 14.73	6.58 / 6.74	>250 dec.	83
7c	$C_{16}H_{12}N_5NaO_6S\cdot 2H_2O$	14.75 / 15.18	6.54 / 6.95	>250 dec.	79
9a	$C_{17}H_{18}N_4O_6S_2\cdot H_2O$	12.40 / 12.27	13.88 / 14.05	232-233	72
9b	$C_{17}H_{17}N_5O_6S\cdot H_2O$	15.78 / 16.01	7.05 / 7.33	248-249	68
9c	$C_{16}H_{15}N_5O_6S\cdot H_2O$	16.45 / 16.54	7.35 / 7.57	236-238	75
10a	$C_{19}H_{20}N_4O_6S_2$	12.06 / 12.06	13.49 / 13.81	132-134	59
10b	$C_{18}H_{17}N_5O_6S\cdot H_2O$	—	7.42 / 7.13	197-198	71
10c	$C_{17}H_{15}N_5O_6S\cdot H_2O$	—	7.49 / 7.36	126-128	58



8, **9**	**a**	**b**	**c**
Ar	C_6H_4Me-4	C_6H_4Me-4	Ph
R	$SO_2C_6H_4Me$-4	$C_6H_4NO_2$-4	$C_6H_4NO_2$-4
R^1	H	Me	Me

In order to check the structure of heterocycles **6a-c**, the methyl derivatives of these compounds were synthesized. Thus, the reaction of **6a** with methyl iodide gave a compound, whose ^{1}H NMR spectrum displayed four-proton doublets at 7.75 and 7.42 ppm and six-proton singlets at 3.14 and 2.39 ppm. The IR spectrum of this product had a carbonyl group stretching band at 1703 cm^{-1} but lacked the diazo group stretching band.



10 a R^1 = Me, R^2 = Ts; **b** R^1 = Me, R^2 = $C_6H_4NO_2$-4; **c** R^1 = H, R^2 = $C_6H_4NO_2$-4

These spectral data indicated that methylation occurred at the carbamoyl nitrogen group and $N_{(2)}$ in the triazole ring. If the reaction had occurred at the oxygen atom and $N_{(3)}$, we would have expected compounds, for which the signal of the OCH_3 or N^+CH_3 group would be observed downfield in the vicinity of 4 ppm [7]. The reaction of **6b,c** with an excess of methyl iodide gave compounds identified as 2-methyl-1-sulfonyl-1,2,3-triazolidin-5-ones **10b,c** as indicated by the ^{1}H NMR, IR, and mass spectra.

Thus, the cyclization of N-arylsulfonyldiazoacetamides by the action of bases leads to sodium 1-arylsulfonyl-1,2,3-triazole-5-olates. This reaction is estimated to be reversible and the triazolates isomerize to diazomalonimidolates in solution upon heating or prolonged maintenance. The acylic isomer is more stable. 5-Hydroxy-1-arylsulfonyl-1,2,3-triazoles, formed in the reaction of 1-arylsulfonyl-1,2,3-triazol-5-olates with acid, rearrange to diazomalonamides, which decompose in DMSO solution to give the corresponding ketones.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on Bruker WR-80 and Bruker 250 spectrometers with TMS as the internal standard. The IR spectra were taken on an IR-75 spectrometer in KBr pellets. The course of the reactions and purity of the products were monitored by thin-layer chromatography on Silufol UV-254 plates with chloroform, 3:1 ethyl acetate–hexane, 9:1 chloroform–ethanol, and 60:11:1 chloroform–ethanol–25% aq. ammonia as the eluents. The melting points were not corrected.

Monoethyl Ester of N-Phenylsulfonylmalonamic Acid (3a). A mixture of benzenesulfonylamide (45.2 g, 0.3 mol), acid chloride of the monoethyl ester of malonic acid (47.2 g, 0.3 mol), and dry benzene (60 ml) was heated at 65-70°C for 15-20 h until completely dissolved. The reaction mixture was then cooled and

filtered through a 1-cm layer of silica gel. The benzene solution was extracted with dilute aqueous ammonia. The aqueous solution was brought to pH 2 and **3a** was isolated as an oil, which gradually crystallized. The product was recrystallized from carbon tetrachloride to give 50.1 g **3a**. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 12.18 (1H, br. s, SO_2NH); 7.60-8.05 (5H, m, Ph); 4.04 (2H, q, *J* = 7.3, OCH_2); 3.35 (1H, s, CH_2); 1.11 (3H, t, *J* = 7.3, CH_3). IR spectrum, ν, cm^{-1}: 3435, 3117 (NH), 2990, 2895 (CH), 1734 (CO_2Et), 1702 ($CONHSO_2$).

Monoethyl Ester of N-Tosylmalonamic Acid (3b) was obtained analogously to **3a**. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm, *J* (Hz): 12.2 (1H, br. s, SO_2NH); 7.85 (2H, d, ArH); 7.70 (2H, d, ArH); 4.04 (2H, q, *J* = 7.3, OCH_2); 3.35 (1H, s, CH_2); 2.29 (3H, s, $ArCH_3$); 1.11 (3H, t, *J* = 7.3, CH_3). IR spectrum, ν, cm^{-1}: 3430, 3120 (NH), 2990, 2895 (CH), 1735 (CO_2Et), 1700 ($CONHSO_2$).

N-Phenylsulfonylmalonamic Acid (4a). A sample of **3a** (17 g, 62.7 mmol) in a solution of KOH (7.41 g, 132 mmol) in water (20 ml) was heated for 3 h at 80°C. The reaction mixture was cooled to room temperature and acidified to pH 2 by adding 1 N hydrochloric acid. The precipitated oil, which crystallized upon cooling, was filtered off, washed with a small amount of cold water, dried in the air, and crystallized from chloroform to give 12.6 g **4a**. IR spectrum, ν, cm^{-1}: 3545 (OH), 3450, 3030 (NH), 2990, 2895, 2776 (CH), 1705 ($CONHSO_2$), 1700 (CO_2H).

N-Tosylmalonamic Acid (4b) was obtained analogously to **4a**.

N,N'-Ditosylmalonamide (5a) was obtained analogously to **3a** by heating malonyl chloride (14.1 g, 0.1 mol) in benzene (60 ml) with tosylamide (34.2 g, 0.2 mol). Yield of **5a** 28.7 g.

N-Aryl-N'-arylsulfonylmalonamides (5b,c). General Method. A sample of dicyclohexylcarbodiimide (2.37 g, 11.5 mmol) was added in portions with stirring to a solution of acid **4a** or **4b** (0.01 mol) and corresponding aniline (0.01 mol) in dry dioxane (15 ml). The mixture was stirred for 10-15 h. The dicyclohexylurea precipitated was filtered off and washed with dioxane (2 ml). The solution obtained was brought to pH 2-3 by adding 1 N hydrochloric acid and diluted with water (60 ml). The precipitated oil gradually crystallized. The product was filtered off and reprecipitated from 10% aqueous ammonia by adding 1 N hydrochloric acid to pH 2-3. The product was recrystallized from aqueous dioxane.

Sodium 4-N-arylcarbimidoyl-1-arylsulfonyl-1,2,3-triazole-5-olate (6a-c). General Method. A solution of sodium (0.23 g, 10 mmol) in absolute ethanol (5 ml) was added with stirring to a solution or suspension of malonamide **5a-c** (5 mmol) in absolute ethanol (20 ml) at room temperature and, then, benzenesulfonylazide (1 g, 5.5 mmol) was added. The mixture was left at room temperature for 24 h. The precipitate formed was filtered off, washed with ethanol (2 ml), and dried over phosphorus pentoxide in vacuum.

Sodium N-Aryl-N'-sulfonyldiazomalonimidolates (7a-c). General Method. A sample of malonamide **5a-c** (5 mmol) in absolute ethanol or CCl_4 (20 ml) was heated at reflux for 4-8 h and then cooled. The precipitate formed was filtered off and dried over phosphorus pentoxide in vacuum.

2-Hydrazono-N-aryl-N'-arylsulfonylmalonamides (9a-c). General Method. A sample of diazomalonamide **1a-c** (5 mmol) in DMSO (2 ml) was heated at 85°C for 4 h. The reaction mixture was cooled and 10% aqueous hydrazine hydrate (30 ml) was added. The precipitate formed was filtered off, crystallized from ethanol, and dried over phosphorus pentoxide in vacuum.

4-(N-Methyl-N-arylcarbamoyl)-2-methyl-1-arylsulfonyl-1,2,3-triazolidin-5-one (10a-c). General Method. A sample of methyl iodide (1.0 ml, 16 mmol) was added to a suspension of triazolate **6a-c** (5 mmol) in dry acetonitrile (30 ml) and stirred for 3 h at room temperature. The precipitate was filtered off, crystallized from ethanol, and dried over phosphorus pentoxide in vacuum.

This work was carried out with the financial support of the Russian Fund for Basic Research, Grant 98-03-33045-a.

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