Theoretical estimation of the possibility of formation of oxadiazocines in the nucleophilic addition of resorcinol to pyrimidines and synthesis of new azoloannelated benzooxadiazocines

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A method was proposed for estimating the possibility of cyclization of adducts of resorcinol with pyrimidines to form oxadiazocines based on the conformational criterion and analysis of charges on the C(5) atom of the pyrimidine ring and on the H atom of the hydroxy group of the resulting adducts. A series of new derivatives of 4,5-dihydro-11*H*-5,11-methanobenzo[*g*]azolo[1,3,5]oxadiazocines were synthesized.

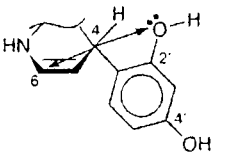
Key words: resorcinol, azolo[1,5-*a*]pyrimidines, 5,11-dihydro-4*H*-5,11-methanobenzo[*g*]azolo[1,3,5]oxadiazocines, σ-adduct, cyclization, molecular mechanics, strain energy, quantum-chemical calculations, electron density distribution.

Aromatic electron-excess compounds (indoles, furans, pyrroles, thiophenes, phenols and their ethers, *etc.*) add to pyrimidine systems under conditions of acid catalysis.[1] In most cases, these reactions afford rather stable σ-adducts and can be used for direct functionalization of various pyrimidine derivatives with fragments of aromatic and heteroaromatic compounds. When binucleophilic agents are used, the adducts that formed initially can undergo further conversions. Thus the reactions of pyrimidine derivatives (**1a,b**) and quinazoline (**1c,d**) with resorcinol (**2**) are stopped in the stage of formation of adducts (**3a—d**) (Scheme 1), while the reactions of other pyrimidines (**1e—i**) give oxadiazocines (**4e—i**). The possibility of the synthesis of these cage structures attracts attention from the viewpoint of the novelty of the resulting heterocyclic systems as well as of their potential biological activity. The synthetic potential of this reaction is still not completely realized, because reactions of resorcinol with annelated heterocycles containing the pyrimidine ring have not been studied yet.

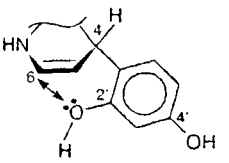
The aim of the present work was, first, to search for calculation criteria which would allow the prediction of the possibility of resorcinol adducts with pyrimidine systems undergoing cyclization and, second, to search for reaction conditions and to prepare new structures by the reactions of azoloannelated pyrimidines with resorcinol.

In the theoretical studies of the possibility of cyclization of resorcinol adducts with pyrimidine systems, we considered the structures of adducts **3a—i**, for which experimental data are available in the literature,[1,2] and the structures of adducts **6a—f**, the possibility of cyclization of which was examined in the present work.

The geometries of molecules **3a—i** were optimized and the strain energies were calculated by molecular mechanics (the MM+ method).[3,4] It was found that two energetically most favorable conformations of the adduct (**A** and **B**) are those in which the resorcinol fragment is perpendicular to the pyrimidine ring. In conformation **A**, the hydroxy group at the C(2′) atom of the resorcinol fragment is far removed from the C(6) electrophilic center, which decreases the probability of cyclization, while conformation **B** seems to be optimum, because in this case two reaction centers, *viz.*, the OH group and the C(6) atom, are in close proximity.



A



B

d^{a}(O(2′)—C(6′)) = 4.67—5.13 Å

d^{b}(O(2′)—C(6)) = 3.20—3.51 Å

The strain energies of two alternative conformations (**A** and **B**) of adducts **3a—i** and the differences between the strain energies

$$\Delta E = E_A - E_B$$

are given in Table 1.

For compounds **3a—d**, conformation **A** is preferable. According to the published data,[1,2] these adducts do not

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Table 1. Strain energies of the molecular conformations (**A** and **B**) of adducts **3a—i** and **6a—f** calculated by the MM+ method

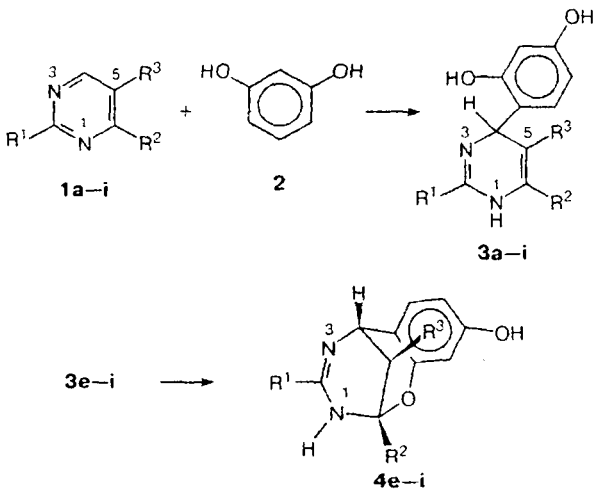
Compound	E_B	E_A	ΔE
	kcal mol^{-1}		
3a	0.490	0.224	0.266
3b	4.951	3.701	1.250
3c	3.683	2.472	1.211
3d	3.814	2.568	1.245
3e	2.650	3.214	−0.564
3f	−10.811	−10.602	−0.209
3g	−6.521	−6.141	−0.380
3h	1.946	2.612	−0.666
3i	−3.330	−2.817	−0.514
6a	28.605	29.401	−0.795
6b	15.485	15.422	0.063
6c	20.416	21.651	−1.236
6d	18.886	20.190	−1.304
6e	5.133	6.054	−0.921
6f	28.878	30.508	−1.630

undergo cyclization. For compounds **3e—i**, conformation **B**, suitable for cyclization, is energetically more favorable. This is in complete agreement with the experimental data.[1,2] More recently, geometry optimization by the *ab initio* quantum-chemical method with the STO-3G basis set demonstrated that the MM+ method adequately reflects the conformational state and tendencies for a change in the energy parameters of the compounds under consideration. Since this method is substantially faster, this can be used for the theoretical estimation and practical prediction of the possibility of cyclization. In addition, the correctness of the predicted conformations of a number of analogous compounds was confirmed by the data of X-ray diffraction analysis.[5] Thus, it follows that the conformational state of the adducts obtained in the reactions of pyrimidines with resorcinol can be considered as the criterion for the possibility of their further cyclization.

In addition to the conformational state of the adducts, which is a reliable criterion for the cyclization, the electron density distribution in the structures under consideration is also of importance. Hence, analysis of the electron density distribution is of great interest. To estimate this distribution, we calculated charges on atoms by the *ab initio* quantum-chemical method with the STO-3G basis set (Table 2).

It was found that the adducts that are able to undergo cyclization differ from those whose reactions with resorcinol are stopped at the stage of addition in the electron density distribution on the atoms adjacent to the reaction center of cyclization. Generally, adducts **3e—i** that undergo further cyclization carry a higher negative charge on the C(5) atom of the pyrimidine ring. This can be characterized as a favorable alternation of the electron density in the pyrimidine ring, which enhances the electrophilicity of the C(6) reaction center. In addition, structures **3e—i** are characterized by a higher charge

Scheme 1

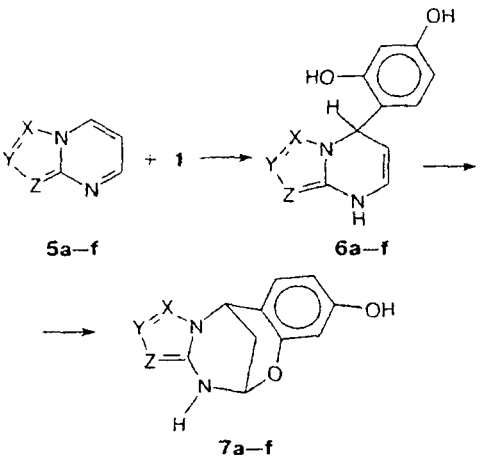


a: $R^1 = R^2 = H$, $R^3 = Me$; **b:** $R^1 = R^2 = R^3 = H$;

c: $R^1 = H$, R^2--R^3 =  ;

d: $R^1 = Me$, R^2--R^3 =  ; **e:** $R^1 = R^3 = H$, $R^2 = Ph$;

f: $R^1 = NH_2$, $R^2 = Me$, $R^3 = H$;
g: $R^1 = NH_2$, $R^2 = R^3 = H$; **h:** $R^1 = R^3 = H$, $R^2 = Me$;
i: $R^1 = R^2 = Me$, $R^3 = H$



a: X = N, Y = CH, Z = CCO_2Et; **b:** X = Y = CCN, Z = N;
c: X = Z = N, Y = CH; **d:** X = Z = N, Y = CSMe;
e: X = Z = N, Y = CCF_3; **f:** X = Y = Z = N

(compared to structures **3a—d**) on the H atom of the OH group of resorcinol, which is the reaction center of cyclization.

Thus, the possibility of cyclization of pyrimidine systems with resorcinol can be predicted from the conformational state of the adduct taking into account the electron density distribution on the C(5) atom of the

pyrimidine ring and on the H atom of the OH group of the resorcinol fragment.

Table 2. Charges (q) on atoms in adducts **3a—i** and **6a—f** (*ab initio*, STO-3G basis set)

Compound	q (au)				
	C(4)	C(5)	O	C(6)	H
3a	0.031	−0.031	−0.333	0.042	0.239
3b	0.032	−0.104	−0.333	0.050	0.237
3c	0.025	−0.032	−0.332	0.114	0.237
3d	0.028	−0.032	−0.332	0.113	0.237
3e	0.028	−0.084	−0.335	0.097	0.242
3f	0.036	−0.114	−0.334	0.114	0.239
3g	0.033	−0.098	−0.336	0.047	0.241
3h	0.029	−0.107	−0.336	0.113	0.242
3i	0.027	−0.103	−0.335	0.109	0.239
6a	0.071	−0.107	−0.330	0.063	0.240
6b	0.071	−0.104	−0.326	0.063	0.239
6c	0.073	−0.107	−0.330	0.064	0.240
6d	0.074	−0.106	−0.330	0.064	0.240
6e	0.073	−0.105	−0.328	0.065	0.238
6f	0.074	−0.102	−0.327	0.066	0.237

Table 3. Reaction conditions and the yields of products **7a—f**

Compound	Reaction conditions				Yield of the product (%)	
	Solvent	Catalyst[a]	τ/h	T/°C	A[b]	B[c]
7a	CF_3CO_2H		72	20	30	19[d]
	MeOH	$BF_3 \cdot Et_2O$	48	20	81	63[d]
7b	MeOH	$BF_3 \cdot Et_2O$	72	20	68	45[e]
7c	CF_3CO_2H		12	20	26	15[f]
	MeOH	HCl	720	20	60	51[f]
	MeOH	CF_3SO_3H	336	20	84	62[f]
	MeOH	$HClO_4$	336	20	76	56[f]
	MeCN	$BF_3 \cdot Et_2O$	12	20	47	30[f]
	MeOH	$BF_3 \cdot Et_2O$	20	20	76	67[f]
	MeOH	$HClO_4$	7	boiling	32	17[f]
	MeOH	$BF_3 \cdot Et_2O$	120	20	72	66[f]
	MeOH	$BF_3 \cdot Et_2O$	18	boiling	98	71[f]
	MeCN	CF_3SO_3H	288	20	67	39[f]
7d	CF_3CO_2H		36	20	15	10[d]
	MeOH	$BF_3 \cdot Et_2O$	120	20	79	65[d]
7e	CF_3CO_2H		3	0	80	65[g]
	MeOH	$BF_3 \cdot Et_2O$	72	20	36	15[e]
7f	CF_3CO_2H		4	0	20	15[e,f]
	MeOH	$BF_3 \cdot Et_2O$	24	20	71	42[e]

[a] Protic acids were taken in an equimolar ratio, 1 mL of $BF_3 \cdot Et_2O$ per mmole of azolopyrimidine.
[b] Crude product.
[c] Purified product.
[d] Recrystallization from EtOH.
[e] Column chromatography.
[f] Recrystallization from MeOH.
[g] Recrystallization from a 1 : 5 EtOH—CCl_4 mixture.

We used the conformational and charge criteria found in this work for estimating the possibility of cyclization of adducts of azoloannelated pyrimidines **6a—f** formed in the reactions of compounds **5a—f** with resorcinol under analogous conditions.[1,2] The geometries of structures **6a—f** were optimized and the strain energies of the molecules were calculated by molecular mechanics (MM+). The charges on atoms were calculated by *ab initio* quantum-chemical methods with the STO-3G basis set (Table 3).

It was established that for azolopyrimidine adducts **6a—f**, conformation **B**, in which the reaction centers, *viz.*, the *ortho*-OH group and the C(6) atom, are in close proximity, is energetically more favorable. This counts in favor of cyclization of the latter with resorcinol. The C(5) atoms adjacent to the cyclization centers (C(6)) carry higher negative charges than the corresponding atoms in compounds **3a—d**, which do not undergo cyclization. Generally, charges on the H atoms of the OH groups in azoloannelated adducts **6a—f** are higher than the corresponding charges in compounds **3a—d**, which also counts in favor of cyclization.

It can be seen from Fig. 1 that the compounds that undergo cyclization and the compounds whose reactions are stopped at the stage of formation of adducts are clearly separated on the ΔE—q(C(5))—q(H) coordinates.

Thus, based on the conformational criterion and the charges on the C(5) atom of the pyrimidine ring and on the H atom of the OH group of the resorcinol fragment, cyclization of adducts with resorcinol would be expected to occur in the case of azolopyrimidines.

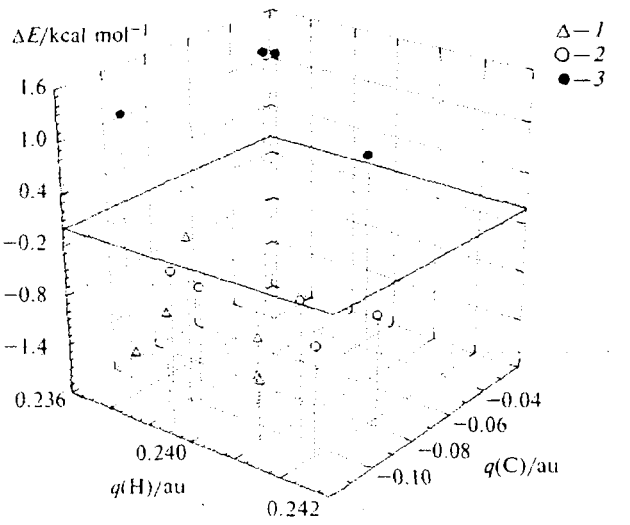


Fig. 1. Arrangement of the compounds on the ΔE—q(C(5))—q(H) coordinates: *1*, azolopyrimidine adducts **6a—f**; *2*, pyrimidine adducts **3e—i** that undergo cyclization; *3*, pyrimidine adducts **3a—d** that do not undergo cyclization.

Table 4. Melting points and the data of elemental analysis and ^{1}H NMR spectroscopy for compounds **7a—f**

Compound	M.p. /°C	Found / Calculated (%)			Molecular formula	^{1}H NMR (DMSO-d_6), δ, *J*/Hz
		C	H	N		
7a	>260	59.51 59.60	5.43 5.30	13.59 13.91	$C_{15}H_{16}N_3O_4$	9.52 (s, 1 H, OH); 8.04 (d, 1 H, NH, $J_{4,5}$ = 4.4); 7.40 (s, 1 H, H(2)); 7.06 (d, 1 H, H(10)); 6.34—6.23 (m, 2 H, H(7), H(9)); 5.72 (m, 1 H, H(5)); 5.30 (m, 1 H, H(11)); 2.28 (m, 2 H, CH_2); 4.12 (q, 2 H, Et); 1.22 (t, 3 H, Et)
7b	137—145	60.64 60.22	3.21 3.23	25.27 25.09	$C_{14}H_9N_5O_2$	9.68 (s, 1 H, OH); 9.39 (d, 1 H, NH, $J_{4,5}$ = 4.7); 7.04 (d, 1 H, H(10)); 6.40 (dd, 1 H, H(9)); 6.27 (d, 1 H, H(7)); 5.76 (m, 1 H, H(5)); 5.47 (m, 1 H, H(11)); 2.38 (m, 2 H, CH_2)
7c	>260	57.41 57.39	4.55 4.35	23.93 24.35	$C_{11}H_{10}N_4O_2$	9.51 (s, 1 H, OH); 8.61 (d, 1 H, NH, $J_{4,5}$ = 4.2); 7.36 (s, 1 H, H(2)); 7.06 (d, 1 H, H(10)); 6.33—6.20 (m, 2 H, H(7), H(9)); 5.70 (m, 1 H, H(5)); 5.32 (m, 1 H, H(11)); 2.31 (m, 2 H, CH_2)
7d	>260	52.26 52.17	4.46 4.35	20.15 20.29	$C_{12}H_{12}N_4O_2S$	9.53 (s, 1 H, OH); 8.67 (d, 1 H, NH, $J_{4,5}$ = 4.2); 7.06 (d, 1 H, H(10)); 6.34—6.23 (m, 2 H, H(7), H(9)); 5.69 (m, 1 H, H(5)); 5.26 (m, 1 H, H(11)); 2.40 (s, 3 H, SMe); 2.31 (m, 2 H, CH_2)
7e	135—137	48.22 48.32	2.97 3.02	18.50 18.79	$C_{12}H_9N_4O_2F_3$	9.59 (s, 1 H, OH); 9.09 (d, 1 H, NH, $J_{4,5}$ = 4.0); 7.13 (d, 1 H, H(10)); 6.37—6.26 (m, 2 H, H(7), H(9)); 5.78 (m, 1 H, H(5)); 5.49 (m, 1 H, H(11)); 2.38 (m, 2 H, CH_2)
7f	>260	51.94 51.95	4.22 3.90	30.17 30.30	$C_{10}H_9N_5O_2$	9.63 (s, 1 H, OH); 9.19 (d, 1 H, NH, $J_{4,5}$ = 4.0); 7.17 (d, 1 H, H(10)); 6.38—6.23 (m, 2 H, H(7), H(9)); 5.95—5.76 (m, 2 H, H(5), H(11)); 2.41—2.31 (m, 2 H, CH_2)

Our studies demonstrated that azolopyrimidines **5a—f** react with resorcinol **1** under conditions of acid catalysis to form cyclization products (**7a—f**).

Generally, the reactions with trifluoroacetic acid as a catalyst afford the target products in low yields and are accompanied by substantial resinification. With the aim of optimizing the reaction conditions and of increasing the yields of the products, we have tested a number of other protic acids in combination with protic (MeOH) and aprotic (MeCN) solvents. In addition, we proposed a Lewis acid (BF_3) as a catalyst, which in most cases allowed us to obtain the desired products in the highest yields. The reaction conditions used and the yields of products **7a—f** are given in Table 3.

The resulting compounds were identified by ^{1}H NMR spectroscopy (Table 4). In the low-field regions of the ^{1}H NMR spectra of oxadiazocines **7a—f**, the signals of the OH and NH groups are observed as a singlet and a doublet, respectively, which disappear when CD_3CO_2D is added into a tube. The characteristic resonance signals of the resorcinol fragment are observed in the region of aromatic protons. The nonresolved multiplet signals for the H(5) and H(11) protons are observed at δ 5.2—5.9. The assignment of the latter was made based on the chemical shifts and the results of experiments on deuterium exchange of mobile protons. In all the cases, the lower-field signal has a poorly resolved spin-spin coupling constant with the NH protons, which disappears upon addition of CD_3CO_2D, while the second signal remains unchanged. The resonance signals for the protons of the CH_2 group are observed as a nonresolved multiplet at δ 2.3—2.4. The spectrum of tetrazoloannealated product **7f** differs from the spectra of the remaining compounds in that the signals for the H(5) and H(11) protons are manifested as a common multiplet. This distinguishing feature may be associated with the presence of azide-tetrazole tautomerism in compound **7f**. However, the IR spectrum of compound **7f** in Nujol mulls shows the presence of only the tetrazole form, while absorption bands in the 2120—2180 cm^{-1} region are absent.

Experimental

The ^{1}H NMR spectra were recorded on Tesla BS-567 A (100 MHz) and Tesla BS-587A (80 MHz) spectrometers in DMSO-d_6 with Me_4Si as the internal standard. The IR spectra were obtained on a UR-20 instrument.

Ethyl 8-hydroxy-5,11-dihydro-4*H*-5,11-methanobenzo[*g*]pyrazolo[5,1-*d*][1,3,5]oxadiazocine-3-carboxylate (**7a**), 8-hydroxy-5,11-dihydro-4*H*-5,11-methanobenzo[*g*]imidazo[2,1-*d*][1,3,5]oxadiazocine-1,2-dicarbonitrile (**7b**), 8-hydroxy-5,11-dihydro-4*H*-5,11-methanobenzo[*g*][1,2,4]triazolo[3,2-*d*][1,3,5]-oxadiazocine (**7c**), 8-hydroxy-2-methylthio-5,11-dihydro-4*H*-5,11-methanobenzo[*g*][1,2,4]triazolo[3,2-*d*][1,3,5]oxadiazocine (**7d**), 8-hydroxy-2-trifluoromethyl-5,11-dihydro-4*H*-5,11-methanobenzo[*g*][1,2,4]triazolo[2,3-*d*][1,3,5]oxadiazocine (**7e**), and 8-hydroxy-5,11-dihydro-4*H*-5,11-methanobenzo[*g*]tetrazolo[5,1-*d*][1,3,5]oxadiazocine (**7f**) were prepared according to a procedure described below.

Azolopyrimidine (1 mmol) and resorcinol (1 mmol, 110 mg) were dissolved in the corresponding solvent. Then a catalyst was added and the reaction mixture was kept at the temperature specified for a predetermined period of time (see Table 3). The solvent was distilled off *in vacuo* and the residue was diluted with water (10 mL) and neutralized with $NaHCO_3$. The crystalline precipitate was filtered off, washed on a filter with water, and dried in air. The yields of the crude and analytically pure products obtained after recrystallization from the corresponding solvent or after column chromatography on silica gel (a 9 : 1 $CHCl_3$—MeOH mixture as the eluent) are given in Table 3.

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