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Structure and Tautomerism of 4-Substituted 3(5)-Aminopyrazoles in Solution and in the Solid State: NMR Study and *Ab Initio* Calculations

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Abstract—Annular tautomerism of 3(5)-aminopyrazoles containing a cyano, thiocyanato, or aryl substituent in the 4-position has been studied by ^{1}H and ^{13}C NMR in solution, cross-polarization and magic-angle spinning ^{13}C NMR in the solid state, and *ab initio* quantum chemical calculations (B3LYP/6-31G**). The title compounds in the solid state exist as 3-amino tautomers. A rare case of slow (on the NMR time scale) annular prototropic tautomerism has been observed in DMSO-d_6: signals of particular tautomers (3- and 5-aminopyrazoles) have been detected in the NMR spectra. 4-Cyano and 4-thiocyanato derivatives exist preferentially as 5-amino tautomers, whereas 4-methoxy analog is represented mainly by the 3-amino tautomers. *Ab initio* calculations (B3LYP/6-31G**) for the gas phase and DMSO solution (in terms of the polarizable continuum model) have shown increase of the relative stability of more polar 5-amino tautomer in going to DMSO.

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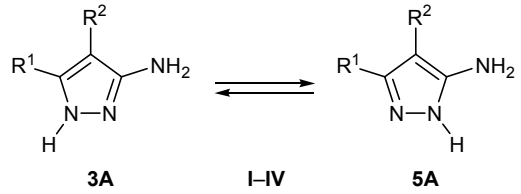
3(5)-Aminopyrazoles are important intermediate products in the synthesis of heterocyclic compounds exhibiting diverse biological activity [1, 2]. The spectrum of biological activity of N-unsubstituted 3(5)-aminopyrazoles also continuously extends. These compounds have recently been shown to act as potential inhibitors of Aurora C kinase and protein kinases C and exhibit antitumor and antimicrobial activity [3–9].

3(5)-Aminopyrazoles having no substituent on the endocyclic nitrogen atom are potentially tautomeric [10–14]. Processes involving proton transfer are responsible for many chemical, physicochemical, and biological properties of these heterocycles. Determination of the molecular and supramolecular structures of 3(5)-aminopyrazoles is important not only for detailed studies of mechanisms of their reactions, where the reactivity may be controlled by a particular tautomeric form. It is also necessary from the viewpoint of molecular recognition problem and structure–biological activity correlations. Despite obvious significance and topicality of quantitative studies on protolytic equilibria of nitrogen heterocycles for prediction of their reactivity, chemical properties, biological activity, and complexing ability, as well as for structure determination of metal coordination compounds derived therefrom [15], relevant systematic data remain insufficient.

Annular tautomerism in the series of 3(5)-amino-1*H*-pyrazoles in solution under normal conditions is a very fast process [10–14], and spectral parameters of particular tautomers can generally be determined only at low temperature [10, 11]. However, 3(5)-amino-5(3)-phenylpyrazole displayed signals from two tautomers in the ^{1}H and ^{13}C NMR spectra in DMSO-d_6 at room temperature. Increase in the electron-withdrawing power of the X-substituent in 3(5)-amino-5(3)-(X-phenyl)pyrazoles was shown to raise the fraction of the 5-amino tautomer [16]. We previously identified signals belonging to different tautomers in the ^{1}H and ^{13}C NMR spectra of 3(5)-amino-5(3)-R^{1}-4-cyanopyrazoles and 3(5)-amino-5(3)-R^{1}-4-thiocyanatopyrazoles in DMSO-d_6 at 20°C [17]. Elguero et al. [18, 19] determined the ^{1}H and ^{13}C chemical shifts and the ratio of 3- and 5-aryl tautomers of 4-halo-3(5)-arylpyrazoles in THF-d_8 at –82°C and DMSO-d_6 at 27°C. Kusakiewicz-Dawid et al. [20] revealed the presence of two tautomers of ethyl 3(5)-amino-5(3)-methylpyrazole-4-carboxylate in DMSO-d_6.

In the present work we examined by NMR spectroscopy how the substituent in position *4* of the heterocycle of 3(5)-amino-5(3)-R^{1}-4-R^{2}-pyrazoles **I**–**IV** affects their tautomer composition (Scheme 1) in solution and in the solid state and estimated the

Scheme 1.



I, R^2 = CN, R^1 = H (**a**), Me (**b**), 4-MeC_6H_4 (**c**), Ph (**d**); **II**, R^2 = SCN, R^1 = 4-$MeOC_6H_4$ (**a**), 4-MeC_6H_4 (**b**), Ph (**c**), 4-BrC_6H_4 (**d**), 4-ClC_6H_4 (**e**); **III**, R^1 = H, R^2 = 4-$MeOC_6H_4$ (**a**), Ph (**b**), 4-ClC_6H_4 (**c**), 3-BrC_6H_4 (**d**); **IV**, R^1 = Me, R^2 = 4-$MeOC_6H_4$ (**a**), Ph (**b**), 4-ClC_6H_4 (**c**), 3-ClC_6H_4 (**d**).

stability of particular tautomers by *ab initio* quantum chemical calculations.

Depending on the substituent nature, 3(5)-amino-5(3)-arylpyrazoles in crystal may exist as one or two tautomers [16, 21]. The cross-polarization magic-angle spinning (CPMAS) ^{13}C NMR spectra of crystalline 4-substituted 3(5)-aminopyrazoles **Id**, **IIId**, and **IVd** are given in Table 1. The spectra contain only one set of signals which may be assigned to tautomer **3A**. The structure of the tautomers was identified by comparing the chemical shifts of the CNH_2 and CR^1 endocyclic carbon atoms in **Id**, **IIId**, and **IVd** with those observed in the CPMAS ^{13}C NMR spectrum of 5-amino-1-(cyclohexylmethyl)-3-methyl-4-phenyl-1*H*-pyrazole (**V-5A**), as well as with the ^{13}C NMR chemical shifts of 5- and 3-amino-substituted pyrazoles **VI**–**XIII** in DMSO-d_6 (Table 2). Similarity between the chemical shifts of the ring carbon atoms in pyrazoles in solution and in the solid state was noted in [22].

The structure of 5-amino-1-benzyl-4-cyano-3-phenyl-1*H*-pyrazole (**VI**) was determined taking into account couplings between the *ortho* protons in the phenyl ring on C^3 and C^3 (δ_C 149.30 ppm, $^3J_{CH}$ = 3.6 Hz) and between protons in the 1-CH_2 group and C^5 (δ_C 153.39 ppm, $^3J_{CH}$ = 2.5 Hz). The ^{13}C chemical shifts of 1-benzyl-4-phenyl-1*H*-pyrazol-5- and -3-amines **VIII** and **IX** were reported by us in [23], while the data for aminopyrazoles **XI**–**XIII** were taken from [16, 24].

The positions of the CR^1 and CNH_2 signals in the CPMAS ^{13}C NMR spectra of **Id**, **IIId**, and **IVd** are

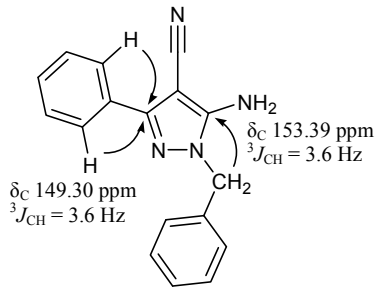
Table 1. Solid-state CPMAS ^{13}C NMR spectra of pyrazoles **Id**, **IIId**, and **IVd** (tautomer **3A**) and 1-(cyclohexylmethyl)-3-methyl-4-phenyl-1*H*-pyrazole (**V-5A**)

Compound no.	R^1	R^2	Chemical shifts δ_C, ppm			
			CR^1	C^4	CNH_2	R^1, R^2
Id-3A	Ph	CN	145.77	74.59	159.93	113.74 (CN), 128.15 (C_6H_5)
IIId-3A	H	3-BrC_6H_4	131.58	107.32	152.01	119.03, 124.56, 127.84, 131.58 (C_6H_4)
IVd-3A	Me	3-ClC_6H_4	139.16	103.16	153.07	10.99 (CH_3), 126.03, 132.26, 135.04 (C_6H_4)
V-5A	Me	Ph	144.60	102.78	144.60	11.39 (CH_3), 25.60, 26.94, 30.25, 30.19, 38.50 (C_6H_{11}), 53.97 (CH_2), 125.87, 128.85, 134.53 (C_6H_5)

Table 2. Chemical shifts of the CR^1 and CNH_2 carbon atoms in the ^{13}C NMR spectra of pyrazoles **VI**–**XIII** in DMSO-d_6

Compound no.	Tautomer	R^1	R^2	N-R	δ_C, ppm	
					CR^1	CNH_2
VI	**5A**	Ph	CN	CH_2Ph	149.30	153.39
VII	**5A**	4-MeC_6H_4	SCN	CH_2Ph	151.20	152.60
VIII[a]	**5A**	H	Ph	CH_2Ph	137.20	143.20
IX[a]	**3A**	H	Ph	CH_2Ph	129.10	152.40
X	**5A**	Me	Ph	CH_2Ph	144.07	143.90
XI[b]	**5A**	Me	H	Bu	147.10	145.00
XII[b]	**3A**	Me	H	Bu	138.30	152.80
XIII[c]	**5A**	Ph	H	H	149.50	149.50
	3A	Ph	H	H	142.40	156.20

[a] Data of [23]; [b] data of [24]; [c] data of [16].



close to those observed for the 3-amino tautomers of structurally related compounds **IX**, **XII**, and **XIII** but are considerably different from the positions of the corresponding signals of model 5-amino derivatives **VI**, **VIII**, **X**, **XI**, and **XIII**. The difference in the δ_C values of the CR^1 and CNH_2 carbon atoms for **Id**, **IIIc**, and **IVa** exceeds 10 ppm, which also confirms the 3-amino structure of these compounds: the corresponding difference for 5-aminopyrazoles is at least twice as low [12, 16, 17, 23].

Thus, compounds **Id**, **IIId**, and **IVd** in the solid state exists as tautomers **3A**. According to the X-ray diffraction data, 4-cyano-substituted amino pyrazoles **Ia** and **Ib** [21] and ethyl 3(5)-amino-5(3)-methylpyrazole-4-carboxylate [20] in crystal also have the structure of 3-amino tautomers **3A**.

The ratio of tautomers of **I**–**IV** in DMSO-d_6 at 20°C was determined by ^{1}H and ^{13}C NMR (Table 3). The spectra of 3(5)-amino-5(3)-aryl-4-cyanopyrazoles **Ic** and **Id** and 3(5)-amino-5(3)-aryl-4-thiocyanatopyrazoles **IIa** and **IIb** contained double signals from the NH and NH_2 protons, and compound **Ic** displayed double signals from the CR^1 and CNH_2 carbon atoms in the ^{13}C NMR spectrum (Fig. 1). We failed to identify carbon signals belonging to the minor tautomer of **Id**, **IIa**, and **IIb** because of its low concentration and signal broadening. The observed signals were assigned by comparing with the spectra of model 3-amino- and 5-aminopyrazoles (Table 2) [17]. In all cases, tautomer **5A** predominates in solution, whereas crystalline compounds **Ia**, **Ib**, and **IIb** are represented by 3-amino tautomer **3A** [21].

As follows from the tautomer ratio of **Ia**–**Id**, **IIa**–**IIe**, and 3(5)-amino-5(3)-arylpyrazoles [16], introduction of an electron-withdrawing substituent (such as

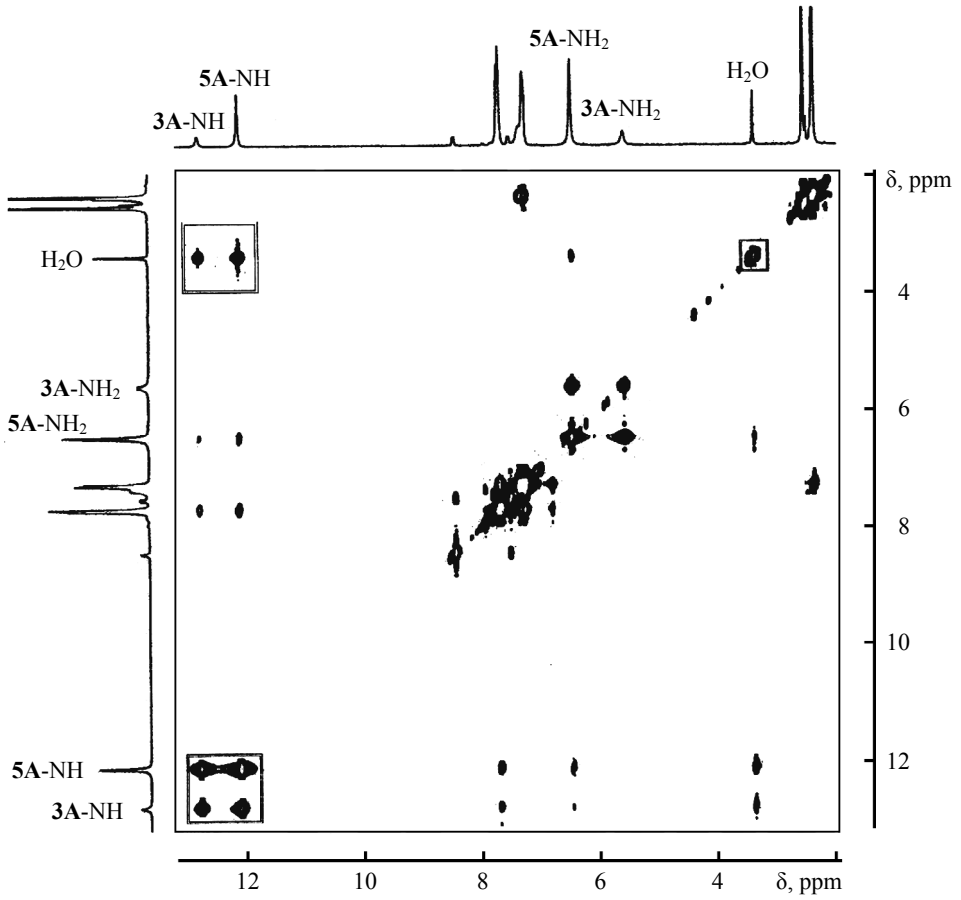


Fig. 1. NOESY spectrum of 5(3)-amino-3(5)-(4-methylphenyl)-1*H*-pyrazole-4-carbonitrile in DMSO-d_6.

CN or SCN group) into position *4* of the pyrazole ring induces considerable shift of the equilibrium toward tautomer **5A**. The NOESY–EXSY experiment for 5(3)-amino-3(5)-(4-methylphenyl)-1*H*-pyrazole-4-carbonitrile (**IIId**) showed that proton transfer between the endocyclic nitrogen atoms in DMSO-d_6 is mediated by water molecules.

4-Aryl-substituted aminopyrazoles **IIIb**, **IIIc**, and **IVa**–**IVc** in DMSO-d_6 displayed in the ^{1}H and ^{13}C NMR spectra only one set of signals, and the NH_2 (δ ~4.5 ppm) and NH signals (δ ~11.5 ppm) in the ^{1}H NMR spectra and CR^1 and CNH_2 signals in the ^{13}C NMR spectra were broadened. The spectral pattern did not change in going to DMF-d_7 at –20 or –40°C. The observed signal broadening indicates the existence of tautomeric equilibrium with fairly high rate of the mutual transformation **3A** ⇄ **5A**, so that the average signals of both tautomers are observed in the ^{1}H and ^{13}C NMR spectra. We succeeded in detecting signals of particular tautomers only in the ^{1}H and ^{13}C NMR spectra of 4-(4-methoxyphenyl)-1*H*-pyrazol-3(5)-amine (**IIIa**) in DMSO-d_6, where the fraction of tautomer **3A** was 70%.

The ratios of tautomers **3A** and **5A** in solutions of 4-aryl-substituted aminopyrazoles **IIIb**–**IIId** and **IVa**–**IVd** were estimated according to the additivity scheme with the use of model compounds [17, 21, 23] and increments of substituents in the pyrazole ring taken from [12]. All the examined 4-aryl-substituted aminopyrazoles in DMSO exist mainly as tautomer **3A** (~60–70%). This very approximate estimate is quite consistent with the experimental data for compound **IIIa**.

Thus, the most favorable tautomer of 4-aryl-substituted 3(5)-aminopyrazoles in DMSO solution is **3A**, whereas aminopyrazoles having an electron-withdrawing substituent on C^4 (CN or SCN group) exist mainly as tautomer **5A**.

With a view to estimate energy parameters of particular tautomers and compare them with the experimental compositions of tautomeric mixtures, the molecular structure of 4-substituted aminopyrazoles **I**–**IV** was simulated by quantum chemical methods. The calculations were performed *ab initio* at the B3LYP/6-31G** level of theory with the use of the polarizable continuum model (PCM) to include solvent effects (see Experimental). The calculation results for tautomers **3A** and **5A** of pyrazoles **Ia**, **Ib**, and **IIIb** are presented in Tables 4 and 5.

In all calculated structures atoms in the pyrazole ring lie in one plane, and the dihedral angle between the pyrazole ring plane and HNH plane of the amino group does not exceed 4°. The N^1H hydrogen atom does not deviate from the pyrazole ring plane. The dihedral angle between the phenyl ring on C^4 and the pyrazole ring in aminopyrazole **IIIb** in the gas phase is larger by ~9° for tautomer **3A** than for **5A**, and it insignificantly decreases for both tautomers in going to DMSO solution (~2°).

Table 3. Tautomeric composition of 3(5)-amino-5(3)-R^1-4-R^2-1*H*-pyrazoles (DMSO-d_6, 20°C)

Compound no.	R^1	R^2	**5A**, %	**3A**, %
Ia[a]	H	CN	100	–
Ib[a]	Me	CN	63	37
Ic	4-MeC_6H_4	CN	75	25
Id	Ph	CN	72	28
IIa	4-$MeOC_6H_4$	SCN	70	30
IIb	4-MeC_6H_4	SCN	76	24
IIc[a]	Ph	SCN	81	19
IId[a]	4-BrC_6H_4	SCN	82	18
IIe[a]	4-ClC_6H_4	SCN	87	13
IIIa	H	4-$MeOC_6H_4$	30	70

[a] Data of [17].

The calculated geometric parameters of pyrazoles **Ia** and **Ib** are consistent with the X-ray diffraction data [21]. The bond lengths and bond angles in the pyrazole ring of each tautomer (**3A** and **5A**) change insignificantly on variation of the 4-substituent: the difference in the bond lengths does not exceed 0.5–0.7% (Table 5). The maximum electron density in tautomers **3A** and **5A** is localized on the amino nitrogen atom. The negative charge in the pyrazole ring is localized mainly on the nitrogen atoms; in going from the gas phase to DMSO solution, the charge on N(H) remains almost unchanged, whereas the charge on N^2 increases in both tautomers. The orders of bonds in the pyrazole ring indicate essential π-electron density delocalization both in the gas phase and in solution.

The calculated (B3LYP/6-31G**) total energies of tautomers **3A** and **5A** of **Ia**, **Ib**, and **IIIb** in the gas phase and DMSO solution are given in Table 4. Tautomers **3A** turned out to be more stable than **5A** in the gas phase; the energy difference between the tautomers of 4-cyano derivatives is ~1 kcal/mol, and it attains ~2 kcal/mol for 4-phenyl-substituted aminopyrazole **IIIb**. These data are in a good agreement with the existence of compounds **Ia**, **Ib**, and **IIIc** in crystal as tauto-

Table 4. Calculated (B3LYP/6-31G**) total energies, zero-point vibration energies, Gibbs energies, enthalpies, differences in the Gibbs energies and enthalpies, and dipole moments of tautomers **3A** and **5A** of aminopyrazoles **Ia**, **Ib**, and **IIIb** in the gas phase and DMSO solution[a]

Compound no.		E_{tot}, hartree	*ZPE*	G°_{298}, kcal/mol	H°_{298}, kcal/mol	ΔE_{tot}, kcal/mol	ΔG°_{298}, kcal/mol	ΔH°_{298}, kcal/mol	μ, D	Δμ, D
Ia (gas phase)	**3A**	–373.60446	54.553	35.137	59.434	–1.1734	0.023	–0.075	4.224	0.943
	5A	–373.60259	54.595	35.114	59.509	0	0	0	5.167	
Ia (DMSO)	**3A**	–373.62199	54.682	35.324	59.484	–0.3326	0.871	0.420	5.558	1.635
	5A	–373.62146	54.045	34.453	59.064	0	0	0	7.193	
Ib (gas phase)	**3A**	–412.90091	71.849	50.120	77.95	–1.255	–1.083	0.051	4.307	0.494
	5A	–412.89891	71.929	51.203	77.899	0	0	0	4.801	
Ib (DMSO)	**3A**	–412.91827	72.342	51.632	78.171	–0.3953	0.199	0.135	5.617	0.903
	5A	–412.91764	72.125	51.433	78.036	0	0	0	6.720	
IIIb (gas phase)	**3A**	–512.32144	106.333	84.269	112.944	–2.303	0.212	0.051	1.673	1.598
	5A	–512.31777	106.226	84.057	112.893	0	0	0	3.271	
IIIb (DMSO)	**3A**	–512.33445	106.612	84.590	113.143	–1.3617	0.123	0.085	2.331	2.141
	5A	–512.33228	106.496	84.467	113.058	0	0	0	4.472	

[a] The data for DMSO solution were obtained using the polarizable continuum model (PCM).

mers **3A**, which was determined experimentally (see above). In DMSO solution the difference in the stabilities of tautomers **3A** and **5A** is smaller, and the ΔE_{tot} value for aminopyrazoles **Ia** and **Ib** becomes negligible. The small energy difference between tautomers suggests that the tautomeric equilibrium could readily be displaced in any direction by intermolecular interactions in solution. The state of tautomeric equilibrium can be roughly estimated on the basis of dipole moments (Table 4, Fig. 2). Both in the gas phase and in

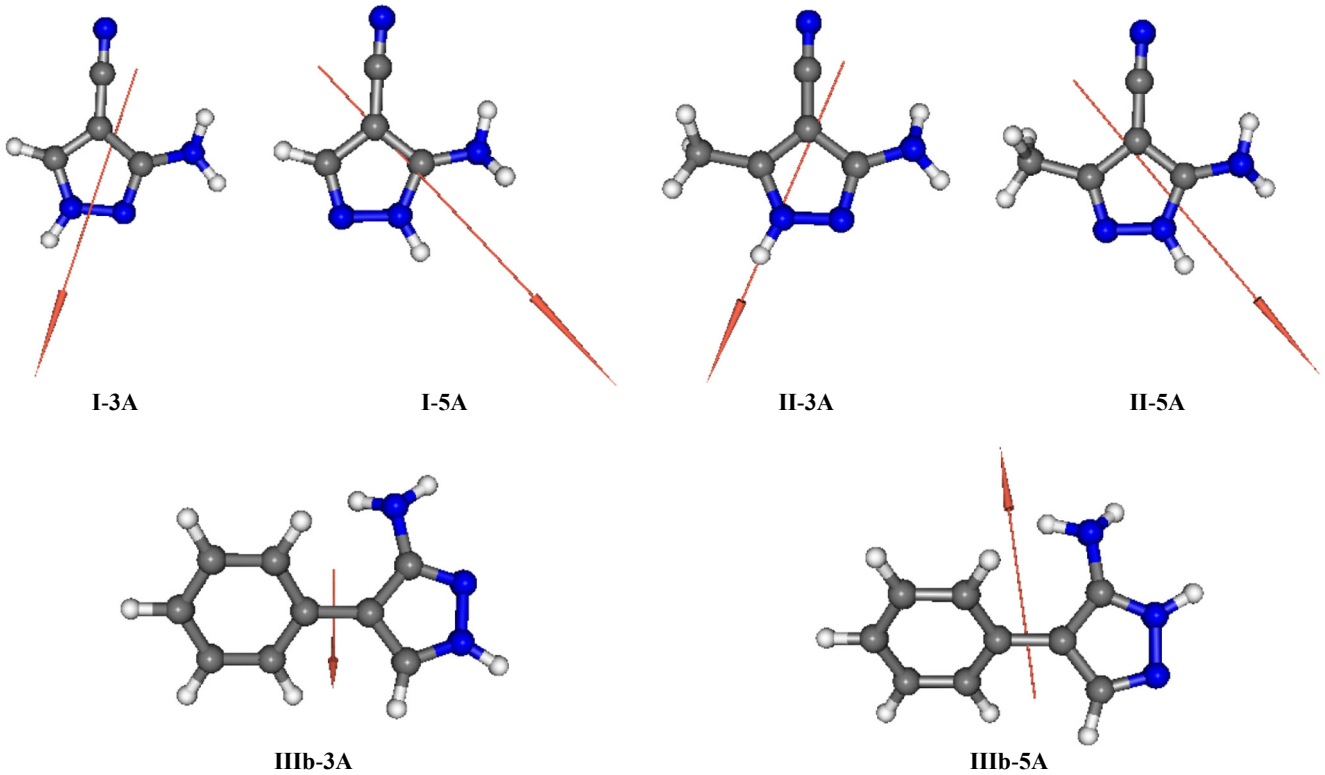


Fig. 2. Calculated (B3LYP/6-31G**) dipole moment vectors of tautomers **3A** and **5A** of aminopyrazoles **Ia**, **Ib**, and **IIIb**.

Table 5. Bond lengths, bond orders, and charges on atoms in the pyrazole ring in tautomers **3A** and **5A** of aminopyrazoles **Ia**, **Ib**, and **IIIb**, calculated at the B3LYP/6-31G** level of theory for the gas phase and DMSO solution (using the polarizable continuum model)

Parameter	Ia				Ib				IIIb			
	gas phase		DMSO		gas phase		DMSO		gas phase		DMSO	
	3A	**5A**	**3A**	**5A**	**3A**	**5A**	**3A**	**5A**	**3A**	**5A**	**3A**	**5A**
Bond lengths in the pyrazole ring and amino group (*d*, Å)												
N–H[a]	1.007	1.008	1.010	1.010	1.008	1.008	1.011	1.010	1.007	1.008	1.008	1.010
N–N	1.366	1.372	1.368	1.376	1.369	1.374	1.371	1.378	1.361	1.367	1.363	1.369
N–C(R^1)	1.343	1.319	1.337	1.319	1.346	1.322	1.341	1.321	1.351	1.325	1.347	1.328
C(R^1)–C(R^2)	1.392	1.427	1.396	1.427	1.398	1.435	1.403	1.435	1.389	1.424	1.392	1.422
C(R^2) –C(NH_2)	1.435	1.401	1.436	1.409	1.434	1.399	1.435	1.408	1.433	1.397	1.433	1.403
N–C(NH_2)	1.330	1.353	1.331	1.351	1.328	1.352	1.330	1.350	1.331	1.358	1.334	1.357
C–NH_2	1.379	1.379	1.381	1.364	1.380	1.379	1.381	1.367	1.397	1.395	1.398	1.387
N–H[b]	1.011	1.013	1.013	1.011	1.011	1.012	1.013	1.012	1.014	1.015	1.015	1.015
N[b]–H	1.011	1.012	1.013	1.012	1.011	1.013	1.012	1.012	1.014	1.014	1.015	1.014
C–R^1	1.080	1.081	1.080	1.082	1.493	1.495	1.492	1.495	1.081	1.083	1.080	1.083
C–R^2	1.414	1.413	1.411	1.408	1.413	1.412	1.409	1.407	1.469	1.467	1.470	1.468
Orders of bonds in the pyrazole ring and amino group												
N–H[a]	0.891	0.894	0.870	0.875	0.895	0.896	0.876	0.877	0.897	0.898	0.879	0.881
N–N	1.141	1.133	1.139	1.126	1.129	1.117	1.127	1.112	1.149	1.146	1.147	1.144
N–C(R^1)	1.153	1.507	1.194	1.510	1.084	1.466	1.121	1.470	1.106	1.479	1.135	1.463
C(R^1)–C(R^2)	1.427	1.280	1.393	1.280	1.403	1.264	1.367	1.263	1.462	1.305	1.441	1.320
C(R^2)–C(NH_2)	1.278	1.379	1.275	1.336	1.259	1.367	1.255	1.323	1.301	1.415	1.307	1.390
N–C(NH_2)	1.390	1.063	1.389	1.079	1.394	1.060	1.392	1.075	1.397	1.040	1.387	1.057
C–NH_2	1.030	1.025	1.041	1.067	1.025	1.018	1.037	1.059	0.990	0.993	1.000	1.017
N–H[b]	0.892	0.887	0.884	0.879	0.893	0.888	0.885	0.879	0.894	0.885	0.885	0.878
N–H[b]	0.894	0.895	0.884	0.878	0.894	0.895	0.884	0.879	0.896	0.899	0.888	0.884
C–R^1	0.936	0.949	0.928	0.945	1.025	1.027	1.031	1.027	0.936	0.949	0.931	0.946
C–R^2	0.962	0.967	0.978	0.991	0.966	0.965	0.984	0.990	1.032	1.023	1.035	1.033
Mulliken charges on atoms in the pyrazole ring and amino group												
(N)H[a]	+0.289	+0.282	+0.326	+0.317	+0.279	+0.278	+0.315	+0.314	+0.275	+0.270	+0.310	+0.303
N(H)[a]	–0.329	–0.401	–0.322	–0.404	–0.395	–0.407	–0.389	–0.409	–0.341	–0.402	–0.340	–0.404
N	–0.381	–0.292	–0.413	–0.336	–0.385	–0.352	–0.421	–0.395	–0.386	–0.310	–0.429	–0.364
C(R^1)	+0.151	+0.129	+0.161	+0.118	+0.380	+0.326	+0.392	+0.327	+0.105	+0.086	+0.098	+0.060
C(R^2)	+0.022	+0.010	–0.001	–0.010	–0.010	–0.001	–0.027	–0.021	–0.047	–0.067	–0.059	–0.073
C(NH_2)	+0.504	+0.547	+0.497	+0.580	+0.508	+0.554	+0.502	+0.583	+0.435	+0.479	+0.420	+0.489
NH_2	–0.659	–0.663	–0.678	–0.675	–0.659	–0.664	–0.679	–0.675	–0.662	–0.663	–0.683	–0.681
H[c]	+0.276	+0.292	+0.294	+0.310	+0.274	+0.291	+0.292	+0.309	+0.259	+0.270	+0.279	+0.290
H[c]	+0.274	+0.273	+0.293	+0.310	+0.273	+0.272	+0.292	+0.309	+0.264	+0.260	+0.280	+0.294

[a] Nitrogen atom in the pyrazole ring.
[b] Nitrogen atom in the amino group.
[c] Hydrogen atom in the amino group.

DMSO solution the dipole moments of tautomeric 4-cyano-substituted aminopyrazoles **Ia** and **Ib** are larger than those for 4-phenyl analog **IIIb**, and the dipole moments of tautomers **3A** are always smaller than the dipole moments of **5A**. The dipole moment of all structures increases in going from the gas phase to polar DMSO, but the observed increase for tautomer **3A** is considerably smaller than for more polar (and hence solvated more efficiently) tautomer **5A**. Presumably, tautomer **5A** of **Ia** and **Ib** should predominate in such polar solvent as DMSO. 4-Phenyl-substituted aminopyrazole **IIIb** is characterized by a smaller dipole moment and larger difference in the stability of tautomers **3A** and **5A**; therefore, a larger fraction of tautomer **3A** in the equilibrium mixture in solution may be expected. In fact, the fraction of tautomer **5A** in DMSO for compounds with electron-withdrawing substituents (4-CN, 4-SCN) is 80–100%, whereas 4-aryl-substitued analogs are represented by 60–70% of tautomer **3A**.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 spectrometer at 300.13 and 75.47 MHz, respectively (DMSO-d_6, 22°C); the chemical shifts were measured relative to the residual proton and carbon signals of the deuterated solvent (DMSO-d_5, δ 2.50 ppm; δ_C 39.50 ppm). The solid-phase CPMAS ^{13}C NMR spectra were obtained at 20°C on a Bruker Avance II-500 instrument (125 MHz; contact time 4 ms; rotation speed 10 kHz); samples were placed into zirconium oxide rotors with a diameter of 4 mm. The high-resolution mass spectra were recorded on a Bruker Daltonics microTOF spectrometer (positive electrospray ionization). The elemental compositions were determined on a Hewlett Packard HP-185B CHN analyzer.

Ab initio calculations were carried out using GAMESS-US software package [25]. Initially, geometric parameters were optimized by the Hartree–Fock method with 6-31G basis set, the data obtained were used as starting ones for the optimization at the DFT B3LYP/6-31G** level, and thermodynamic parameters were calculated for the optimized structures. The same structures were used as input data in the DFT B3LYP/6-31G** calculations with inclusion of solvent effects in terms of the PCM model [26], and thermodynamic parameters were calculated from the results. In all cases, geometric parameters were optimized without symmetry restrictions, and local minima on the potential energy surfaces were identified by calculating vibrational frequencies.

Compounds **Ic** and **Id** were synthesized from the corresponding (alkoxyarylmethylidene)malononitriles and hydrazine hydrate according to the procedure described in [27].

3(5)-Amino-5(3)-(4-methylphenyl)-1*H*-pyrazole-4-carbonitrile (Ic). Yield 73%, mp 176–178°C (from MeOH–H_2O); published data [28]: mp 173–178°C (EtOH–H_2O).

Tautomer **3A**. ^{1}H NMR spectrum, δ, ppm: 5.57 br.s (2H, NH_2), 7.26–7.71 m (4H, C_6H_4), 12.76 br.s (1H, N^{1}H). ^{13}C NMR spectrum, δ_C, ppm: 21.71 (CH_3), 117.13 (CN), 143.66 br.s (C^5); 128.36, 131.00, 138.96 (C_{arom}); 159.66 br (C^3); the C^4 signals was not identified because of broadening.

Tautomer **5A**. ^{1}H NMR spectrum, δ, ppm: 6.48 br.s (2H, NH_2), 7.26–7.71 m (4H, C_6H_4), 12.09 br.s (1H, N^{1}H). ^{13}C NMR spectrum, δ_C, ppm: 21.71 (CH_3), 70.28 br (C^4), 117.13 (CN); 126.45, 130.17, 138.90 (C_{arom}); 150.90 br (C^3), 155.30 br (C^5).

3(5)-Amino-5(3)-phenyl-1*H*-pyrazole-4-carbonitrile (Id). Yield 85%, mp 202°C [29].

Tautomer **3A**. ^{1}H NMR spectrum, δ, ppm: 5.60 br.s (2H, NH_2), 7.32–7.85 m (5H, Ph), 12.84 br.s (1H, N^{1}H). The ^{13}C NMR spectrum was not recorded because of the low concentration and signal broadening.

Tautomer **5A**. ^{1}H NMR spectrum, δ, ppm: 6.44 br.s (2H, NH_2), 7.32–7.85 m (5H, Ph), 12.15 br.s (1H, N^{1}H). ^{13}C NMR spectrum, δ_C, ppm: 71.34 br (C^4), 117.06 (CN), 150.09 br (C^3), 156.30 br (C^5); 132.07, 129.65, 126.54 (Ph).

Compounds **IIa** and **IIb** were synthesized according to the procedure described in [30].

5(3)-(4-Methoxyphenyl)-4-thiocynato-1*H*-pyrazol-3(5)-amine (IIa). Yield 73%, mp 146°C, mixture of tautomers. ^{1}H NMR spectrum (DMSO-d_6 + one drop of CF_3COOH), δ, ppm: 5.84 br.s (2H, NH_2); 7.05 m, 7.08 m, 7.69 m, 7.72 m (4H, C_6H_4); 12.17 br.s (1H, N^{1}H). ^{13}C NMR spectrum, δ_C, ppm: 56.07 (OCH_3), 74.57 br (C^4), 114.95 (SCN); 124.18, 129.42, 160.38 (C_{arom}); 149.48 br (C$^{3(5)}$), 155.66 br (CNH_2).

Tautomer **3A**. ^{1}H NMR spectrum, δ, ppm: 5.47 br.s (2H, NH_2), 7.05–7.72 m (4H, C_6H_4), 12.39 br.s (1H, N^{1}H).

Tautomer **5A**. ^{1}H NMR spectrum, δ, ppm: 5.99 br.s (2H, NH_2), 7.05–7.72 m (4H, C_6H_4), 12.11 br.s (1H, N^{1}H). Found, %: C 53.25; H 4.17. $C_{11}H_{10}N_4OS$. Calculated, %: C 53.64; H 4.09.

5(3)-(4-Methylphenyl)-4-thiocyanato-1*H*-pyrazol-3(5)-amine (IIb). Yield 65%, mp 121°C.

Tautomer **3A**. ^{1}H NMR spectrum, δ, ppm: 2.35 s (3H, CH_3), 5.45 br.s (2H, NH_2); 7.29 m, 7.31 m, 7.64 m, 7.67 m (4H, C_6H_4); 12.58 br.s (1H, N^{1}H).

Tautomer **5A**. ^{1}H NMR spectrum, δ, ppm: 2.35 s (3H, CH_3), 6.06 br.s (2H, NH_2); 7.29 m, 7.31 m, 7.64 m, 7.67 m (4H, C_6H_4); 12.12 br.s (1H, N^{1}H). ^{13}C NMR spectrum, δ_C, ppm: 21.74 (CH_3), 72.90 br (C^4), 114.63 s (SCN); 127.99, 130.03, 138.86 (C_{arom}); 148.50 br (C^3), 155.41 br (C^5). Found, %: C 57.07; H 4.58. $C_{11}H_{10}N_4S$. Calculated, %: C 57.37; H 4.38.

3(5)-Amino-5(3)-alkyl-4-aryl-1*H*-pyrazoles IIIa–IIId and IVa–IVd (*general procedure*). Hydrazine hydrate, 50 mmol, was added dropwise to a solution of 25 mmol of the corresponding ketonitrile in 50 mL of ethanol and 5 mL of acetic acid. The mixture was stirred for 2 h at 50°C, an additional 10 mL of acetic acid was added, and the mixture was heated for 5 h under reflux, cooled to room temperature, poured into 200 mL of ice water, and neutralized to pH 9 by adding aqueous ammonia. The precipitate was filtered off, dried in air, and purified by recrystallization.

4-(4-Methoxyphenyl)-1*H*-pyrazol-3(5)-amine (IIIa). Yield 70%, mp 202–203°C (from MeCN), a mixture of tautomers; published data [31]: mp 198–201°C. ^{1}H NMR spectrum, δ, ppm: 3.74 s (3H, CH_3O), 4.52 br.s (1.4H, NH_2 in **3A**), 4.98 br.s (0.6H, NH_2 in **5A**), 6.89–7.43 (4H, C_6H_4), 7.61 br.s (1H, CH), 11.65 br.s (1H, NH).

Tautomer **3A**. ^{13}C NMR spectrum, δ_C, ppm: 106.85 (C^4), 126.84 (CH), 151.42 (CNH_2), 55.01 (CH_3O); 114.02, 126.48, 158.62 (C_6H_4).

Tautomer **5A.** ^{13}C NMR spectrum, δ_C, ppm: 55.01 (CH_3O), 102.52 (C^4), 137.66 (C^3), 143.69 (C^5NH_2); 114.02, 126.48, 158.62 (C_6H_4). Found: *m*/*z* 190.0998 $[M + H]^+$. $C_{10}H_{12}N_3O$. Calculated: $[M + H]^+$ 190.0975.

4-Phenyl-1*H*-pyrazol-3(5)-amine (IIIb). Yield 75%, mp 173–174°C (from MeCN); published data [32]: mp 174–176°C. ^{1}H NMR spectrum, δ, ppm: 4.76 s (2H, NH_2); 7.11 t (1H), 7.32 t (2H), and 7.49 d (2H) (Ph); 7.67 s (1H, CH), 11.69 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 105.62 (C^4), 130.67 (CH), 149.32 (CNH_2); 124.54, 125.47, 130.67, 134.07 (Ph). Found: *m*/*z* 160.0882 $[M + H]^+$. $C_9H_{10}N_3$. Calculated: $[M + H]^+$ 160.0869.

4-(4-Chlorophenyl)-1*H*-pyrazol-3(5)-amine (IIIc). Yield 80%, mp 146–147°C (from MeCN); published data [32]: mp 141–143°C. ^{1}H NMR spectrum, δ, ppm: 4.85 s (2H, NH_2), 7.34–7.55 m (4H, C_6H_4), 7.71 (1H, CH), 11.78 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 105.32 (C^4), 131.81 (CH), 150.25 (CNH_2); 133.88, 129.57, 129.55, 127.86 (C_6H_4). Found: *m*/*z* 194.0493 $[M + H]^+$. $C_9H_9ClN_3$. Calculated: $[M + H]^+$ 194.0480.

4-(3-Bromophenyl)-1*H*-pyrazol-3(5)-amine (IIId). Yield 71%, mp 130–132°C (from MeCN). ^{1}H NMR spectrum, δ, ppm: 4.89 s (2H, NH_2), 7.26–7.76 m (4H, C_6H_4), 7.71 s (1H, CH), 11.79 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 105.15 (C^4), 131.82 (CH), 150.15 (CNH_2); 123.01, 124.97, 127.85, 128.42, 131.40, 137.54 (C_6H_4). Found: *m*/*z* 237.9988 $[M + H]^+$. $C_9H_9BrN_3$. Calculated: $[M + H]^+$ 237.9974.

4-(4-Methoxyphenyl)-3(5)-methyl-1*H*-pyrazol-5(3)-amine (IVa). Yield 71%, mp 139–140°C (from EtOAc). ^{1}H NMR spectrum, δ, ppm: 2.14 s (3H, Me), 3.76 s (3H, CH_3O), 4.42 s (2H, NH_2), 6.93–7.27 m (4H, C_6H_4), 11.09 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 11.92 (CH_3), 55.86 (CH_3O), 104.79 (C^4), 137.90 (**C**Me), 151.70 (CNH_2); 114.86, 127.17, 129.93, 157.76 (C_6H_4). Found: *m*/*z* 204.1144 $[M + H]^+$. $C_{11}H_{14}N_3O$. Calculated: $[M + H]^+$ 204.1131.

3(5)-Methyl-4-phenyl-1*H*-pyrazol-5(3)-amine (IVb). Yield 73%, mp 138–139°C (from MeCN); published data [33]: mp 138–140°C. ^{1}H NMR spectrum, δ, ppm: 2.17 s (3H, Me), 4.45 s (2H, NH_2), 7.17–7.39 m (4H, C_6H_4), 11.29 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 11.41 (CH_3), 104.12 (C^4), 138.00 (**C**Me), 150.90 (CNH_2); 125.03, 127.92, 128.62, 134.33 (Ph). Found: *m*/*z* 174.1041 $[M + H]^+$. $C_{10}H_{12}N_3$. Calculated: $[M + H]^+$ 174.1026.

4-(4-Chlorophenyl)-3(5)-methyl-1*H*-pyrazol-5(3)-amine (IVc) [34]**.** ^{1}H NMR spectrum, δ, ppm: 2.17 s (3H, Me), 4.62 s (2H, NH_2), 7.34–7.41 m (4H, C_6H_4), 11.40 s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 12.16 (CH_3), 103.85 (C^4), 138.75 (**C**Me), 151.82 (CNH_2); 129.24, 130.12, 130.27, 133.98 (C_6H_4).

4-(3-Chlorophenyl)-3(5)-methyl-1*H*-pyrazol-5(3)-amine (IVd) [35]**.** Yield 71%, mp 128–131°C. ^{1}H NMR spectrum (DMSO-d_6–CCl_4), δ, ppm: 2.18 s (3H, Me), 4.59 br.s (2H, CH_2), 7.20–7.41 m (4H, C_6H_4), 11.50 br.s (NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 11.39 (Me), 102.88 (C^4), 138.20 (**C**Me), 150.98 (CNH_2); 124.60, 126.24, 127.11, 130.19, 133.22, 136.54 (C_6H_4). Found: *m*/*z* 208.0649 $[M + H]^+$. $C_{10}H_{10}ClN_3$. Calculated: $[M + H]^+$ 208.0637.

1-(Cyclohexylmethyl)-3-methyl-4-phenyl-1*H*-pyrazol-5-amine (V). Yield 87%, mp 129°C. ^{1}H NMR spectrum, δ, ppm: 0.83–1.89 m (11H, C_6H_{11}), 2.08 s

(3H, Me), 3.69 d (2H, CH_2, J = 7.3 Hz), 5.00 (NH_2), 7.10–7.40 m (5H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 13.47 (Me); 25.35, 26.09, 30.03, 37.72 (C_6H_{11}); 52.04 (CH_2), 101.33 (C^4), 143.02 q (C^3, ^2J = 6.5 Hz), 143.62 br (C^5); 124.52, 127.81, 128.47, 134.57 (Ph). Found: m/z 270.1980 $[M + H]^+$. $C_{17}H_{23}N_3$. Calculated: $[M + H]^+$ 270.1966.

5-Amino-1-benzyl-3-phenyl-1*H*-pyrazole-4-carbonitrile (VI) [36]**.** Yield 85%, mp 170–172°C. ^1H NMR spectrum, δ, ppm: 5.25 (2H, CH_2), 6.90 (2H, NH_2), 7.24 (2H), 7.29 (1H), 7.34 (2H), 7.39 (1H), 7.44 (2H), 7.81 (2H). ^{13}C NMR spectrum, δ_C, ppm: 50.15 t.t (CH_2, J = 139.5, 3.6 Hz), 70.01 t (C^4, ^3J = 3.3 Hz), 115.98 (CN), 131.55 t (J = 7.6 Hz); 128.74, 127.48, 125.70, 127.28, 128.54, 136.57 (C_{arom}); 149.30 t (C^3, ^3J = 3.6 Hz), 153.39 t (C^5, ^3J = 2.5 Hz). Found, %: C 74.23; H 5.35. $C_{17}H_{14}N_4$. Calculated, %: C 74.43; H 5.14.

1-Benzyl-3-(4-methylphenyl)-4-thiocyanato-1*H*-pyrazol-5-amine (VII). Yield 55%, mp 115°C. ^1H NMR spectrum, δ, ppm: 2.34 s (3H, CH_3), 5.25 br.s (2H, NH_2), 6.54 s (2H, CH_2), 7.25–7.70 m (9H, H_{arom}). ^{13}C NMR spectrum, δ_C, ppm: 21.73 (Me), 51.53 (CH_2), 72.72 br (C^4), 113.70 (SCN), 151.20 br (C^3), 152.60 br (C^5); 128.02, 128.29, 129.33, 129.90, 130.19, 137.76, 138.39 (C_{arom}). Found, %: C 67.61; H 5.20. $C_{18}H_{16}N_4S$. Calculated, %: C 67.47; H 5.03.

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