JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. **12**, 470–478 (1999)

^{1}H, ^{13}C and ^{15}N NMR and IR studies of halogen-substituted tetrazolo[1,5-*a*]pyridines

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Received 25 June 1998; revised 4 November 1998; accepted 9 December 1998

ABSTRACT: The tetrazole–azide tautomerization of some halogen-substituted tetrazolo[1,5-*a*]pyridines was examined by IR spectroscopy at ambient temperature and by ^{1}H, ^{13}C and ^{15}N NMR spectroscopy at various temperatures. The tetrazolopyridines can exhibit equilibrium between the azide and the tetrazole forms. For some of them slow exchange occurs on the NMR time-scale, such that it is possible to estimate equilibrium constants. The position and nature of the substituent in the pyridine ring result in stabilization or destabilization of the tetrazole form and exert a strong influence on the values found for the equilibrium constants. A saturation transfer experiment was carried out for 5-bromotetrazolo[1,5-*a*]pyridine and the rate constants were estimated. Moreover, based on the van't Hoff equation, the enthalpy $\Delta H°$ and entropy $\Delta S°$ for the tautomerization were calculated. *Ab initio* calculated energies and charge distribution are in good agreement with differences observed in the tetrazole–azide equilibrium constants. Copyright © 1999 John Wiley & Sons, Ltd.

KEYWORDS: tetrazole; azide; valence tautomerism; IR spectra; ^{1}H, ^{13}C, ^{15}N NMR; *ab initio* calculations protonation

INTRODUCTION

Since the presence of the tetrazole–azide equilibrium in some substituted tetrazolo[1,5-*a*]pyridines has been confirmed by different spectroscopic methods (IR, ^{1}H and ^{13}C NMR),[1–5] we re-examined the halogen derivatives of tetrazolopyridine systems **1–12** by ^{1}H, ^{13}C and ^{15}N NMR and IR studies. In previous work,[6] we reported that saturation transfer takes place for this type of tautomerism. Based on this experiment for one of the compounds we calculated the rate constants for the equilibrium, which confirmed the above statement about a slow exchange. In this paper, we try to explain the influence of some substituents on the tetrazole–azide equilibrium and on the basis of the relationship between temperature and the equilibrium constant we calculated $\Delta H°$, $\Delta S°$ values for this isomerization process. Attention is focused on some regularities in the differences between the spectral parameters such as NMR chemical shifts, coupling constants, longitudinal relaxation times T_1 and IR wavenumbers for both forms in the equilibrium given in Fig. 1. The calculated *ab initio* molecular properties (SCF energies, atom partial charges, NMR shieldings) were tested for their usefulness in the tetrazole–azide tautomerism.

EXPERIMENTAL

Synthesis

The compounds studied were prepared by nucleophilic substitution of the chlorine atom in position 2 with the azide ion (**4–6, 8, 10–12**) and reaction of the corresponding substituted 2-hydrazinopyridine with sodium nitrite in acidic solution (**1–3, 7, 9**). Mass spectra and elemental analysis were used for identification of the products obtained. The data for unknown substituted tetrazolo [1,5-*a*]pyridines are as follows:

2-Azido-6-fluoropyridine (**1**): MS, *m/z* 138, 110, 83, 64; m.p., 50 °C; analysis: calculated for $C_5H_3N_4F$, H 2.17, C 43.48, N 40.58; found, H 1.98, C 42.56, N 39.89%.

5-Bromotetrazolo[1,5-*a*]pyridine (**3**): MS, *m/z* 200, 198, 172, 170, 145, 143, 119, 117, 91, 64; m.p., 118–120 °C; analysis: calculated for $C_5H_3N_4Br$, H 1.51, C 30.15, N 28.14; found, H 1.36, C 30.21, N 29.01%.

6-Chlorotetrazolo[1,5-*a*]pyridine (**4**): MS, *m/z* 156, 154, 128, 126, 101, 99, 91, 64; m.p., 112–113 °C; analysis: calculated for $C_5H_3N_4Cl$, H 1.94, C 38.83, N 36.25; found, H 1.71, C 38.36, N 35.89%.

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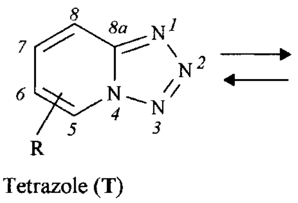
Contract/grant sponsor: Polish State Committee for Scientific Research; *Contract/grant number:* 3 T09 A 010 12.

CCC 0894–3230/99/060470–09 $17.50



1	R = 5-F	**7**	R = 8-Cl
2	R = 5-Cl	**8**	R = 8-I
3	R = 5-Br	**9**	R = 6-Cl, 8-Cl
4	R = 6-Cl	**10**	R = 6-CF_3, 8-Cl
5	R = 6-Br	**11**	R = 6-COOH, 8-Cl
6	R = 6-CF_3	**12**	R = 6-Br, 8-Br, 7-CH_3

Figure 1. Tetrazole–azide tautomerization of different substituted tetrazolo[1,5-*a*]pyridines. Numbering of azides is according to the tetrazole and does not correspond to the IUPAC system

8-Iodotetrazolo[1,5-*a*]pyridine (**8**): MS, *m/z* 246, 218, 191, 165, 127, 91, 64; m.p., 225–226 °C; analysis: calculated for $C_5H_3N_4I$, H 1.22, C 24.39, N 22.76; found, H 1.06, C 23.90, N 22.52%.

6,8-Dibromo-7-methylotetrazolo[1,5-*a*]pyridine (**12**): MS, *m/z* 294, 292, 290, 266, 264, 262, 185, 183, 158, 156, 131, 103, 76, 51; m.p., 116–118 °C; analysis: calculated for $C_6H_4N_4Br_2$, H 1.37, C 24.66, N 19.18; found, H 1.09, C 23.56, N 17.98%.

Spectra

Bruker AM 500 and Bruker 500 DRX spectrometers operating at 500.138, 125.759, 36.45 and 50.684 MHz for ^1H, ^{13}C, ^{14}N and ^{15}N, respectively, were used for measurements of all the spectra. The concentrations of chloroform, DMSO and TFA solutions of compounds studied were between 0.5 and 1 mol dm^{-3}. Usually the spectra were measured at 295 K; in some cases other temperatures were applied. The ^1H NMR spectra for thermodynamic measurements were recorded with relaxation delay $\Delta = 5T_1$. Standard experimental conditions and standard Bruker software for C–H correlations optimized for one-bond couplings (170–190 Hz), INVGATE for ^{15}N NMR measurements, 1D INADEQAUTE optimized for one-bond C–C couplings (65 Hz) and GHMBC correlations for ^{13}C and ^{15}N NMR signal assignment were used. The ^1H and ^{13}C chemical shifts are given relative to the TMS signal at 0.0 ppm. Nitromethane, $\delta = 0$ ppm, was used as an external standard for ^{15}N NMR spectra. For relaxation measurements the inversion–recovery sequence was used and samples were degassed by the pump–thaw procedure to remove paramagnetic oxygen.

Table 1. IR bands (cm^{-1}) of 6,8-dichlorotetrazolo[1,5-*a*]-pyridine (**9**) in KBr pellets and $CHCl_3$ and CCl_4 solutions[a]

KBr	$CHCl_3$ solution	CCl_4 solution
3105–3020	3124–3000	3130–3000
	2138 (m)	2137 ↑
1617 (m)	1619 (w)	
	1568	1567 ↑, 1551
1536 (s)	1535	1533 ↓
1476 (s)	1479	1483 ↓, 1476, 1466, 1451
	1423	1422 ↑
	1381	1381 ↑
1324 (m)	1324	1323 ↓
	1301	1301 ↑
1245 (w)	1247	1245
1210 (w)		1228
1147 (s)	1146, 1124	1155 ↑, 1142 ↓, 1124
1102 (m)	1105	1107 ↓
1073 (s)	1070, 1055	1065 ↓, 1055 ↑
1001 (w)	1002	997 ↓
974 (m)	976	973 ↓
916 (m)		
888 (m)	896, 888, 874	896 ↑, 888 ↓, 874 ↑
842 (m)	826	825
797 (s), 758 (m), 635 (m), 581 (m)		

[a] Band intensities: (s) strong, (m) medium, (w) weak; ↑ ↓, increase or decrease in band intensities on passing from $CHCl_3$ to CCl_4 solution.

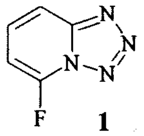
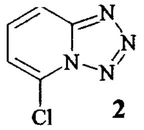
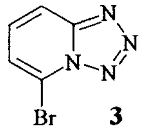
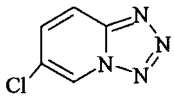
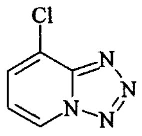
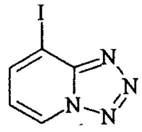
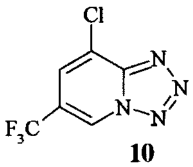
Calculations

The *ab initio* GIAO-CHF molecular orbital calculations were performed on a Silicon Graphics Onyx workstation using the Turbomole program of BIOSYM/MSI.[7] The double-ζ basis with a polarization function $(dz + p)$[8] was used for the geometry optimization of both forms of the tetrazolopyridines studied. The triple-ζ basis set with two polarization functions $(tz + p)$[8] was used for the calculation of SCF electron energy, absolute ^1H, ^{13}C and ^{15}N nuclear shieldings and charge distribution by the Roby–Davidson procedure.[7] The calculations were carried out on isolated molecules in the gas phase with no solvent effects included. Electron correlation was not taken into account, and C_s symmetry was used in each case.

RESULTS AND DISCUSSION

All the compounds studied (except **1**) exist in the solid state as the tetrazole and this is clearly proved by IR spectroscopy of the samples in KBr pellets. The lack of characteristic bands of asymmetric and symmetric stretching vibrations of the azide oscillator for **2**–**12** demonstrate the presence of the tetrazole forms. In the 1350–950 cm^{-1} range typical, but rather weak, tetrazole bands are also of great significance in distinguishing between both these forms. Most characteristic are those at

Table 2. ^{1}H NMR chemical shifts (ppm) and coupling constants (*J*, Hz) for some of the compounds studied

Compound	Atoms	Tetrazole CDCl$_3$	Azide CDCl$_3$	Tetrazole TFA	Azide TFA
 1	H6	—^{c}	6.70	—^{c}	7.26
	H7	—^{c}	7.72	—^{c}	8.24
	H8	—^{c}	6.67	—^{c}	7.02
 2	H6	7.30	7.07	7.31	7.16
	H7	7.68	7.58	7.78	8.00
	H8	8.02	6.72	7.84	7.22
 3	H6	7.46	7.22	7.40	7.23
	^{3}J(H6, H7)	(7.24)	(7.70)	(7.56)	(8.07)
	H7	7.60	7.47	7.62	7.77
	^{3}J(H7, H8)	(8.92)	(7.94)	(8.92)	(8.07)
	H8	8.04	6.75	7.77	7.16
	^{4}J(H6-H8)	(0.92)	(0.68)	(0.62)	(0.56)
 4	H5	8.97	8.29	8.98	8.24
	J^{4}(H5, H7)	(1.80)	(2.57)	(1.70)	(2.40)
	H7	7.73	7.61	8.01	8.27
	^{3}J(H7, H8)	(9.45)	(8.60)	(9.50)	(9.14)
	H8	8.07	6.79	8.10	7.76
	^{5}J(H5, H8)	(0.90)	(0.60)	(0.77)	(0.60)
 7^{a}	H5	8.80	—^{c}	8.42	7.80
	^{3}J(H5, H6)	(6.88)		(6.90)	(6.07)
	H6	7.21	—^{c}	7.00	7.06
	^{3}J(H6, H7)	(7.35)		(7.60)	(8.24)
	H7	7.71	—^{c}	7.54	7.87
	^{4}J(H5, H7)	(0.85)		(0.66)	(1.52)
 8^{b}	H5	9.33	—^{c}	8.51	—^{c}
	H6	7.24	—^{c}	6.85	—^{c}
	H7	8.34	—^{c}	8.02	—^{c}
 10	H5	9.18	8.50	8.61	8.00
	H7	7.89	7.89	7.43	7.69

[a] Data taken from Ref. 6.

[b] Chemical shifts taken on DMSO solution.

[c] Absence of this form in solution.

1330, 1240, 1100 and 1020 cm^{-1}.[9] The low solubility of **8** and **11** in carbon tetrachloride and chloroform is the reason why we cannot ascertain whether they have a tendency to open the tetrazole ring. 8-Chlorotetrazolo-[1,5-*a*]pyridine (**7**) in both solvents exists only in the tetrazole form, whereas in the IR spectra of CCl$_4$ and CHCl$_3$ solutions of all of the remaining compounds the typical bands of both forms are present. When the polarity of the solvent increases (CCl$_4$ $\rightarrow$ CHCl$_3$), the intensity of the 2130 and 1300 cm^{-1} bands becomes weaker. Considering this observation we can assume that the amount of the tetrazole form increases with the increasing solvent polarity. In Table 1, IR bands for 6,8-dichlorotetrazolo[1,5-*a*]pyridine (**9**) in KBr pellets, CCl$_4$ and CHCl$_3$ solutions are presented.

Comparison of the solid-state IR spectrum of **9** with those taken on CHCl$_3$ and CCl$_4$ solutions allowed us, unequivocally, to assign the bands of both forms. In the 1650–850 cm^{-1} region, with a decrease in the solvent polarity the intensities of the 1619, 1535, 1479, 1324, 1146, 1105, 1070, 1002, 976 and 888 cm^{-1} bands decrease and these are connected with oscillations of the tetrazole forms.

Table 3. ^{13}C NMR data for some of the compounds studied

		Tetrazole			Azide				
Compound	Atom	$\sigma_{calc.}$[f]	$\delta_{calc.}$[g]	$CDCl_3$[h]	$\sigma_{calc.}$[f]	$\delta_{calc.}$[g]	$CDCl_3$[h]	Tetrazole TFA[h]	Azide TFA[h]
1	C8a	33.2	152.2	—[i]	25.7	159.7	153.0 [13.3]	—[i]	151.6 [4.0]
	C5	37.3	148.1	—[i]	22.3	163.1	162.6 [244.6]	—[i]	159.6[k]
	C6	101.3	84.1	—[i]	92.1	93.9	104.8 [35.4]	—[i]	105.0 [24.3]
	C7	50.0	135.4	—[i]	36.2	149.2	143.2 [8.1]	—[i]	148.6 [12.0]
	C8	79.4	106.0	—[i]	83.7	101.7	110.7 [4.6]	—[i]	111.0 [4.2]
2[a]	C8a	34.2	151.2	149.2	26.0	159.4	154.5	144.7	153.3
	C5	50.6	134.8	127.4	29.0	156.4	150.2	129.9	143.6
	C6	78.5	106.9	116.3	74.7	110.7	120.1	119.3	121.2
	C7	52.8	132.6	132.4	39.8	145.6	140.7	138.4	148.3
	C8	74.8	110.6	114.2	80.1	105.3	112.2	110.5	113.8
3	C8a	34.2	150.3	149.3	25.9	158.6	154.6	143.6	153.9
	C5	51.0	133.5	115.0	27.3	157.2	140.4	117.5	131.6
	C6	73.6	110.9	120.5 (175.0)	70.5	114.0	123.9 (173.2)	123.8 (180.0)	125.1 (182.2)
	C7	53.2	131.3	132.5 (169.5)	40.5	144.0	140.4 (164.4)	138.9 (174.3)	147.8 (173.2)
	C8	74.1	110.4	114.7 (175.9)	79.5	105.0	112.5 (169.0)	110.4 (185.0)	114.0 (176.3)
4[b]	C8a	36.5	148	147.2	27.3	157.2	152.7	142.1	150.1
	C5	60.9	123.6	123.4 (196.8)	36.4	148.1	147.4 (187.7)	124.2 (201.0)	137.4 (196.6)
	C6	64.1	120.4	125.2	62.1	122.4	127.5	129.1	129.7
	C7	50.7	133.8	133.6 (172.0)	41.7	142.8	138.2 (169.0)	139.5 (176.8)	147.9 (176.2)
	C8	72.7	111.8	116.0 (175.6)	77.1	107.4	114.7 (169.1)	112.5 (184.1)	116.9 (176.2)
7[c]	C8a	36.1	149.3	147.8	29.1	155.4	—[i]	144.8	147.4
	C5	60.3	125.1	124.0 (193.1)	37.2	148.2	—[i]	125.1 (199.4)	138.3 (198.7)
	C6	78.7	106.7	116.5 (171.5)	74.3	111.1	—[i]	119.8 (175.7)	122.4 (179.8)
	C7	53.9	131.5	130.8 (170.7)	41.0	144.4	—[i]	136.3 (174.1)	149.0 (174.8)
	C8	61.3	124.1	123.0	66.6	118.8	—[i]	121.0	128.5
8	C8a	—[j]	—[j]	149.4	—[j]	—[j]	—[i]	146.8	—[i]
	C5	—[j]	—[j]	126.2 (196.1)	—[j]	—[j]	—[i]	126.6	—[i]
	C6	—[j]	—[j]	118.3 (173.2)	—[j]	—[j]	—[i]	120.8	—[i]
	C7	—[j]	—[j]	141.8 (172.2)	—[j]	—[j]	—[i]	148.1	—[i]
	C8	—[j]	—[j]	80.2	—[j]	—[j]	—[i]	73.0	—[i]
9[c,d]	C8a	37.3	148.1	146.7	30.7	154.7	149.9	145.5	146.8
	C5	62.1	123.3	122.2 (198.3)	38.4	147.0	145.3 (189.2)	122.8 (201.6)	137.8
	C6	64.6	120.8	123.1[l]	62.3	123.1	127.4	122.0	130.4
	C7	51.9	133.5	132.4 (176.0)	41.2	144.2	138.1 (172.5)	135.9 (177.4)	147.3
	C8	60.8	124.6	124.9[d]	66.3	119.1	121.0	128.1	128.3
10[e]	C8a	—[j]	—[j]	148.1	—[j]	—[j]	154.9	147.7	—[i]
	C5	—[j]	—[j]	123.2 (196.0)	—[j]	—[j]	143.7 (186.2)	123.8 (174.6)	—[i]
	C6	—[j]	—[j]	121.5	—[j]	—[j]	123.8	124.2	—[i]
	C7	—[j]	—[j]	127.2 (173.0)	—[j]	—[j]	135.6 (169.8)	130.0 (174.6)	—[i]
	C8	—[j]	—[j]	124.5	—[j]	—[j]	120.8	123.8	—[i]
	CF_3	—[j]	—[j]	121.6	—[j]	—[j]	122.6	121.4	—[i]

[a] C–C coupling constants (Hz): ^1J(C8a, C8), T 70.1, A 69.6; ^1J(C5, C6), T 78.7, A 68.4; ^1J(C6, C7), T 52.7, A 53.8; ^1J(C7, C8), T 60.2, A 56.5.

[b] ^1J(C, C) for tetrazole form: ^1J(C8a, C8) 71.5, ^1J(C5, C6) 65.6, ^1J(C6, C7) 61.6, ^1J(C7, C8) 61.5 Hz.

[c] ^{13}C NMR chemical shifts and $^1J(^{13}C, ^1H)$ coupling constants for $CDCl_3$ and tetrazole forms in TFA solutions taken from Ref. 6.

[d] C–C coupling constants (Hz): ^1J(C8a, C8) T 85.1, A not determined; ^1J(C5, C6), T 83.2, A 64.1; ^1J(C6, C7) T 62.8, A 64.8; ^1J(C7, C8) T 72.4, A 66.3.

[e] $^nJ(^{13}C, ^{19}F)$ coupling constants (Hz): in $CDCl_3$, C8aT not determined, C8aA 1.3, C5T 5.5, C5A 4.3, C6T 36.1, C6A 34.0, C7T 2.5, C7A 3.5, C8T and C8A not determined, CF_3T 272.8, CF_3A 272.3; in TFA, C6T 36.7, C7T 2.3, CF_3T 271.9.

[f] $\sigma_{calc.}$ = Calculated *ab initio* ^{13}C absolute shieldings (ppm).

[g] $\delta_{calc.}$ = Calculated chemical shifts (ppm).

[h] Experimental chemical shifts (ppm), with $^nJ(^{13}C, ^{19}F)$ coupling constants in square brachets and $^1J(^{13}C, ^1H)$ coupling constants in parentheses.

[i] No signals because of low concentration or absence of this form.

[j] Not calculated.

[k] Not determined because of overlapping with TFA signal.

[l] Assignment should be reversed compared with our previous paper.[6]

Table 4. ^{15}N NMR data (ppm) for some of the compounds studied

Compound	Atom	Tetrazole			Azide			Tetrazole TFA[f]	Azide TFA[f]
		$\sigma_{calc.}$[d]	$\delta_{calc.}$[e]	δ(DMSO)[f]	$\sigma_{calc.}$[d]	$\delta_{calc.}$[e]	δ(DMSO)[f]		
1[a]	N1	−63.2	−71.8	—[g]	161.1	−296.1	−275.2	—[g]	—[h]
	N2	−210.9	+75.9	—[g]	6.1	−141.1	−143.2	—[g]	—[h]
	N3	−108.3	−26.7	—[g]	−13.1	−121.9	—[i]	—[g]	—[h]
	N4	12.0	−147.0	—[g]	5.0	−140.0	−130.4	—[g]	—[h]
2	N1	−66.7	−68.3	−64.4	162.4	−297.4	−274.5	−135.0	−274.2
	N2	−207.7	+72.7	+17.9	6.3	−141.3	−141.3	−10.1	−152.2
	N3	−116.7	−18.3	−32.6	−13.2	−121.8	−143.0	−36.2	−132.2
	N4	0.7	−135.7	−129.0	−27.0	−108.0	−102.3	−131.1	−199.3
3	N1	−67.4	−67.6	−64.0	162.7	−297.7	−276.1	−137.1	−274.4
	N2	−207.2	+72.2	+17.0	6.3	−141.3	−141.3	−11.3	−152.3
	N3	−119.3	−15.7	−28.8	−13.2	−121.8	−143.0	−32.4	−132.4
	N4	−2.3	−132.7	−127.0	−34.1	−100.9	−94.8	−129.4	−196.3
7	N1	−68.3	−66.7	−67.9	163.6	−298.6	—[g]	−111.6	—[h]
	N2	−207.7	+72.7	+18.2	6.1	−141.1	—[g]	−4.6	−154.0[j]
	N3	−119.6	−15.4	−27.8	−12.2	−122.8	—[g]	−31.3	—[h]
	N4	−1.2	−133.8	−126.6	−36.8	−98.2	—[g]	−129.6	−198.1[j]
9[b]	N1	−69.9	−65.1	−66.3	163.7	−298.7	−276.1	−95.8	—[h]
	N2	−208.2	+73.2	+20.8	6.8	−141.8	−143.3	−7.8	−153.9[j]
	N3	−120.7	−14.3	−27.7	−13.3	−121.7	−141.4	−30.4	—[h]
	N4	0.6	−135.6	−129.8	−38.4	−96.6	−90.8	−130.0	−198.5[j]
10[c]	N1	—[k]	—[k]	−65.6	—[k]	—[k]	−271.9	−89.4	—[h]
	N2	—[k]	—[k]	+24.6	—[k]	—[k]	−144.4	+5.4	−153.6[j]
	N3	—[k]	—[k]	−24.9	—[k]	—[k]	−140.0	−26.7	—[h]
	N4	—[k]	—[k]	−132.2	—[k]	—[k]	−93.6	−132.2	—[h]

[a] ^{15}N NMR chemical shifts in $CDCl_3$, ^{2}J(N4, F) = 51.2 Hz.
[b] ^{15}N NMR chemical shifts in $CDCl_3$ and for the tetrazole form in TFA taken from Ref. 6.
[c] ^{15}N NMR chemical shifts at 323 K in $CDCl_3$.
[d] $\sigma_{calc.}$ = Calculated *ab initio* ^{15}N absolute shieldings (ppm).
[e] $\delta_{calc.}$ = Calculated chemical shifts (ppm).
[f] Experimental chemical shifts (ppm).
[g] No signals because of low concentration or absence of this form.
[h] Not measured.
[i] Not detected in long-range ^{15}N–^{1}H correlation.
[j] From ^{14}N NMR measurements.
[k] Not calculated.

The bands at 2138, 1568, 1423, 1381, 1301, 1055, 896 and 874 cm^{-1} increase in intensity and can be assigned to the azido form.[10] The IR spectra in the solid state and in solutions are useful but only for qualitative estimation. To characterize fully the type of equilibria considered, NMR methods are irreplaceable. Based on the ^{1}H NMR integrals, the equilibrium constants for tetrazole–azide tautomerism (with a maximum 5% error) can be estimated. The ^{15}N NMR signals are of great importance in distinguishing between the tetrazole and azido forms because of the completely different chemical shifts of the nitrogen nuclei in the open and closed forms.[6,11] The ^{1}H, ^{13}C and ^{15}N NMR spectral parameters for some chosen compounds are given in Tables 2–4 (spectral data for all the compounds studied are available on request). Differences in the ^{1}H, ^{13}C and ^{15}N NMR chemical shifts and coupling constants are typical of both the tetrazole and azido forms. They are of great importance in the description of the tetrazole–azide tautomerism and are in good agreement with those published previously.[6,12] Using the Turbomole program we calculated absolute ^{13}C and ^{15}N nuclear shieldings (Tables 3 and 4) for both tetrazole and azido forms for some of the compounds studied to assist the correctness of ^{13}C and ^{15}N signal assignments. Subsequently the ^{13}C and ^{15}N absolute shieldings were recalculated by the use of the equations $\delta_{calc} = 184.5 - \sigma_{abs}$ for ^{13}C and $\delta_{calc} = -135.0 - \sigma_{abs}$ for ^{15}N nuclei[13] (where δ_{calc} is the calculated chemical shift, σ_{abs} the calculated absolute shielding, 184.5 the calculated absolute shielding for ^{13}C nucleus of TMS and −135.0 the calculated absolute shielding for ^{15}N nucleus of nitromethane) to chemical shifts (Tables 3 and 4). These latter parameters correlate very well with the experimental data and the relationships are as follows:

$$\text{for } ^{13}\text{C nuclei: } \delta_{exp.} = 0.763\ \delta_{calc} + 31.559\ (R = 0.98)$$
$$\text{for } ^{15}\text{N nuclei: } \delta_{exp.} = 0.816\ \delta_{calc} - 24.725\ (R = 0.99)$$

where $\delta_{exp.}$ denotes experimental chemical shifts (ppm). Based on these equations or direct correlations between the calculated absolute shieldings and the experimental chemical shifts, signal assignments can be easily made and eventually confirmed.

Table 5. Longitudinal relaxation times T_1 (295 K) for azido (A) and tetrazole (T) form of compounds **2** and **3**

Compound	Atom	T_1 (s)	Atom	T_1 (s)
2	H6A	35.6	C6A	5.4
	H6T	33.5	C6T	4.7
	H7A	17.3	C7A	6.2
	H7T	16.4	C7T	5.5
	H8A	29.9	C8A	6.3
	H8T	27.2	C8T	4.8
3	H6A	25.6	C6A	4.9
	H6T	—[a]	C6T	4.4
	H7A	—[a]	C7A	5.8
	H7T	11.0	C7T	4.9
	H8A	24.3	C8A	5.4
	H8T	18.0	C8T	5.0

[a] Not determined.

Table 6. Tetrazole–azide equilibrium constants (295 K) for the compounds studied

	$K_{T/A}$		
Compounds	CDCl$_3$	DMSO	TFA[h]
1	∞	∞	∞
2	15.30	2.75[a]	2.20/1.80[b]
3	5.95[c]	0.65[d]	0.82
4	0.02	0.00	0.45/0.32[b]
5	0.02	0.00	0.40
6	0.04[e]	0.00	0.27
7	0.00	0.00	0.00/0.04[b]
8	—	0.00	0.00
9	0.31[f]	0.02	0.00/0.03[b]
10	0.34	0.02	0.02
11	—	0.00	0.03
12	0.26[g]	0.02	—

[a] Equilibrium constants $K_{T/A}$: 300 K, 2.75; 319 K, 3.75; 333 K, 4.15; 357 K, 6.72.
[b] Tetrazole–azide equilibrium constants after 2 months.
[c] Equilibrium constants $K_{T/A}$: 308 K, 6.58; 318 K, 7.85; 325 K, 8.88.
[d] Equilibrium constants $K_{T/A}$: 300 K, 0.65; 319 K, 1.16; 333 K, 1.35; 357 K, 2.06.
[e] Equilibrium constants $K_{T/A}$: T 308 K, 0.06; 318 K, 0.08; 325 K, 0.10.
[f] Equilibrium constants $K_{T/A}$: 308 K, 0.41; 318 K, 0.54; 325 K, 0.63.
[g] Equilibrium constants $K_{T/A}$: 308 K, 0.37; 318 K, 0.47; 325 K, 0.56. The deviation in $K_{T/A}$ was about 0.02–0.05.
[h] Azide-to-tetrazole concentration ratio.

From the spectral parameters in Tables 2–4 we conclude that fixation of the tetrazole structure is accompanied by some other changes in NMR data. This statement is supported, for example, by ^1J(C,C) coupling constants for **2** and **9** (footnotes to Table 3). ^1J(C5,C6) and ^1J(C7,C8) are larger for the tetrazole form than the appropriate constants in the azido form by 10 and 4 Hz for **2** and by 20 and 6 Hz for **9**, respectively. In pyridine the corresponding values are 54.3 and 53.7 Hz.[14] Differences in one-bond C–C coupling constants can also be useful in signal assignment of both forms in equilibrium. For **2**, INADEQUATE measurements in addition to ^{1}H–^{13}C one-bond and ^{1}H–^{15}N long-range correlations were used to correct a previously erroneous assignment for H6 and H8 in the azido form.[2] The correct one is given in Table 2.

The differences in structure of both forms in equilibrium also exert some influence on other NMR parameters. For example, Table 5 contains some ^{1}H and ^{13}C longitudinal relaxation time T_1 data for the azido and tetrazole forms of **2** and **3**. In general, these values are longer for the azide than for the corresponding nuclei in the tetrazole form and suggest that molecules of the azido form are more mobile than those of the tetrazole form. Using ^{1}H NMR longitudinal relaxation times T_1 for both H8 protons in tetrazole and azido forms, the results of saturation transfer experiment for **3** and the equations[15]

$$K_{T/A} = k_1/k_{-1} = [A]/[T]$$

$$f_S^A\{S^T\} = -k_{-1}/R_S^A + k_{-1}$$

where $K_{T/A}$ is the equilibrium constant for tetrazole–azide tautomerization, k_1 and k_{-1} are forward and backward first-order rate constants, $[A]$ and $[T]$ are the concentrations of the azido and tetrazole forms, respectively, in equilibrium, $f_S^A\{S^T\}$ is the observed fractional intensity change of a signal of the azide form after saturation of a signal in the tetrazole form, $R_S^A = 1/T_1$ for a chosen proton in the azido form and T_1 is the longitudinal relaxation time of chosen proton, it is possible to calculate the rate constants for the tetrazole–azide equilibrium.

We found for **3** that $k_1 = 0.059 \pm 0.005\ \mathrm{s}^{-1}$ and $k_{-1} = 0.012 \pm 0.005\ \mathrm{s}^{-1}$. Hence, $K_{T/A} = 4.90$ for this compound in CDCl$_3$ solution at 295 K is in good agreement with the equilibrium constant obtained from integration of the ^{1}H NMR spectrum. The values of the rate constant are 100 times larger then those obtained by Krivopalov *et al.*[16] and suggest that in the case of tetrazolopyridines the tetrazole–azide equilibration is faster than in the case of tetrazolopyrimidines. The values of k_1 and k_{-1} indicate that the reaction of opening of the tetrazole ring is about five time faster than the opposite reaction.

Other differences in spectral parameters were observed in the TFA solutions. Here protonation of nitrogen nuclei takes place. For the tetrazole form, in TFA solution the N1, N2, C8a and C8 nuclei are much more shielded (by about 30–70, 30, 1–5 and 1–4 ppm, respectively) than they are in solutions in aprotic solvents. These differences depend strongly on the strength of tetrazole–acid interactions. For the azido form the N4, C8a and C5 nuclei are more shielded in TFA (by about 100, 1–2 and 8–10 ppm, respectively) than they are in aprotic solvents. Protonation effects, in TFA solutions, are also responsible for producing an increase in the chemical shift difference between N2 and N3 of the azide form from

Table 7. Values of enthalpy and entropy of tetrazole–azide tautomerization

Solvent	Compound	ΔH° (kJ mol^{-1})	ΔS° (J mol^{-1} K^{-1})
CDCl$_3$	**3**	10.6 ± 0.5	50.6 ± 2.7
	6	24.1 ± 1.2	54.9 ± 3.3
	9	19.0 ± 1.5	54.6 ± 4.2
	12	20.22 ± 1.2	57.4 ± 3.1
DMSO	**2**	13.5 ± 0.5	53.4 ± 2.5
	3	17.6 ± 0.5	55.5 ± 2.7

2 ppm in CDCl$_3$ solutions to about 20 ppm in TFA. In addition, a change of the aprotic solvent from chloroform to DMSO causes reversal of ^{15}N signal assignment for the N2/N3 nuclei (Table 4). In more polar DMSO the N3 nucleus is much more shielded than the same nucleus in CDCl$_3$.

Since tetrazole–azide tautomerization is slow on the NMR time-scale and based on the differences in NMR data between the two forms, the influence of substituents on this equilibrium can be discussed. In our studies we used deuterated chloroform, DMSO and protonating trifluoroacetic acid (TFA) as solvents. The equilibrium constants for the compounds that potentially have a tendency to equilibrate are collected in Table 6. In chloroform all the molecules (except **7, 8** and **11**) exist as mixtures of both forms, whereas the equilibrium is strongly shifted towards the azido form for 5-halogen-substituted tetrazolopyridines **2** and **3**. 2-Azido-6-fluorpyridine (**1**) can exist only in this form because of the strongly electronegative character of the fluorine atom. When the electronegativity of the halogen atom in position 5 decreases (F, Cl, Br), the amount of the tetrazole form gradually increases. Compounds **4–6** with the same substituents in position 6 do not exhibit the above-mentioned tendency. Introduction of a second halogen atom in position 8 (**9, 10** and **12**) causes an increase in the azido form but the tetrazole form still predominates. Compounds **7** and **8** in aprotic solvents exist as tetrazoles, which suggests that halogen atoms in position 8 stabilize this form. An increase in the polarity of the solvents used is responsible for stabilization of the tetrazole forms. For the compounds studied only the 5-halogen substituted tetrazolopyridines (**2** and **3**) in DMSO exhibit an equilibrium between the two forms. From variable-temperature ^{1}H NMR measurements for selected compounds (in CDCl$_3$ and DMSO solutions) and using the van't Hoff equation $\Delta G^\circ = -RT \ln K_{T/A}$, where $\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$, $K_{T/A}$ is the equilibrium constant, T is the absolute temperature and R is the gas constant, we estimated values of the enthalpy and entropy of tetrazole–azide tautomerization (Table 7). Thermodynamic data for similar compounds have been reported earlier[2,5,17] and our studies confirm only the fact that these equilibria are governed by ΔS. The positive values of entropy are responsible for the existence of the azides in solutions. All tetrazole-to-azide tautomerizations are endothermic but the values of the enthalpy determine the susceptibility of different substituted tetrazolo [1,5-*a*]pyridines to tetrazole–azide tautomerization. The higher the value of the enthalpy, the lower is the tendency for tetrazolopyridine to open its ring. An increase in a solvent polarity (CDCl$_3$ → DMSO) causes an increase in the enthalpy difference between the azido and tetrazole forms (Table 7)[16] and confirms that in more polar solvents the tetrazole form is much more preferred to the azide. A similar tendency can be observed in the case of the nitro-substituted tetrazolopyridines,[18] where this group in position 6 facilitates opening of the tetrazole moiety in the sequence 7-methyl-6-nitro- > 6-nitro- > 8-methyl-6-nitro- > 5-methyl-6-nitrotetrazolo[1,5-*a*]pyridine.

The *ab initio* calculated charge distribution, using the Roby–Davidson approximation, and differences in total SCF energies between the azido and tetrazole forms allow us to explain the behaviour of the halogen-substituted tetrazolopyridines (Table 8). The calculated SCF energies for the azides suggest that this form is much more stable than the tetrazole form. This inconsistency

Table 8. Atomic charges and total SCF energies calculated by *ab initio* method for the chosen compounds

Compound	Form	Total SCF energy (kJ mol^{-1})	Difference in SCF energies (kJ mol^{-1})	Atomic charge (a.u.)				Differences in atomic charges N4–N3
				N1	N2	N3	N4	
1	Tetrazole	−1336739.0	−49.0	−0.3208	−0.0015	−0.1617	0.1480	0.3097
	Azide	−1336788.0		−0.4926	0.6471	−0.2181	−0.3869	−0.1688
2	Tetrazole	−2283360.0	−35.0	−0.3147	−0.0076	−0.1645	0.1760	0.3405
	Azide	−2283395.0		−0.4922	0.6474	−0.2191	−0.3639	−0.1448
4	Tetrazole	−2283370.0	−14.0	−0.3156	−0.0110	−0.1736	0.1960	0.3696
	Azide	−2283384.0		−0.4923	0.6497	−0.2281	−0.3449	−0.1168
7	Tetrazole	−2283367.0	−8.0	−0.3051	−0.0095	−0.1705	0.2016	0.3721
	Azide	−2283375.0		−0.4839	0.6512	−0.2240	−0.3456	−0.1216
9	Tetrazole	−3489988.0	−17.0	−0.3000	−0.0089	−0.1661	0.1991	0.3652
	Azide	−3490005.0		−0.4811	0.6469	−0.2154	−0.3374	−0.1220

Table 9. Tetrazole–azide equilibrium constants after successive addition of TFA to chloroform solution

Compound	Neat	1:1	2:1	3:1
2	15.30	1.73	1.00	0.72
3	5.90	0.72	0.40	0.25
9	0.31	0.11	0.06	0.04

can be explained by taking into account the fact that calculations were carried out on isolated molecules in the gas phase with no solvent effects included. As is known from the work of Wentrup and co-workers[5,10,17] and from other theoretical calculations,[19,20] the azido form is much more stable than the tetrazole form in the gas phase. Differences in calculated SCF energies for both the azide and tetrazole forms are helpful in studying this type of equilibrium. When this difference increases then the tetrazole form has a greater bigger tendency to open its ring. Tetrazole–solvent interactions are responsible for stabilization of the tetrazole form when compared with the gas phase. In fact, the above-mentioned interactions depend on the polarity of the solvent and clearly prove that the differences in energies between the tetrazole and azido forms should be small. Two recent theoretical papers[19,20] were focused on different effects in tetrazole–azide tautomerization and our calculations confirm their results.

The differences in partial charges between the N4 and N3 atoms of the tetrazole form range from 0.3097 a.u. for 2-azido-6-fluoropyridine (**1**) to 0.3721 a.u. for 8-chloro-tetrazolo-pyridine (**7**). The smaller the difference is, the higher is the content of the azido form in the mixture. Partial charges for both forms can be very helpful in the prediction of protonation and alkylation sites.[21] TFA as a polar solvent should stabilize the tetrazole form but must also be considered as a protonating agent. This property in many cases is responsible for the different behaviours of substituted tetrazoloazines. In fact, TFA can be applied in two different ways. When equimolar amounts of it are added to a chloroform solution it behaves only as a polar solvent. This means that in TFA the equilibrium is shifted towards the tetrazole form. The data for this case are presented in Table 9. Dissolution of tetrazolopyridines in a large excess of TFA causes protonation and, in many cases, opening of the tetrazole ring. This latter fact is in accordance with the behaviour of different tetrazoloazines in TFA[22] and implies that the strength of the N3—N4 bond in tetrazoloazines decreases significantly in acidic solutions. In the case of 5-halogen substituted compounds only **1** exists in the azide form. All the remaining solutions in TFA of the compounds studied contain mixtures of the tetrazole and azide forms in different ratios. For 5- and 6-halogen-substituted tetrazolopyridines the values of the azide-to-tetrazole concentration ratio are in the range 0.27–2.20 and can change after some period of time. In the case of **7** and **9** the azido form appears after 2 months, whereas the azide-to-tetrazole concentration ratio for **2** and **4** decrease after the same time. In both protonating and aprotic solvents **1** does not reveal the presence of 5-fluorotetrazolopyridine, whereas 8-chloro- (**7**) and 8-chloro-6-carboxytetrazolopyridine (**11**) exist as tetrazoles only. However, the latter two compounds in excess of TFA undergo opening of the tetrazole ring after 2 months, as is obvious when we observe the ^{14}N or ^{15}N NMR spectra of these compounds. The signals at *ca* -154 and -200 ppm are in typical positions of the N2 and N4 nuclei of the protonated azido form.[6] For almost all of the compounds studied a ‘protonation rate’ is comparable to a ‘ring opening rate,’ but for some of them, namely **8, 11** (and others with substituents in positions 6 and 6, 8), the former is significantly faster. Hence we have postulated that at first protonation occurs and is followed by opening of the tetrazole ring. All the investigated 6-substituted tetrazolopyridines in aprotic solvents exist decidedly as tetrazoles, whereas the introduction of a second chlorine atom in position 8 shifts the equilibrium towards the azido form, although the tetrazole form still predominates. The reverse is observed in TFA solution (Table 6). 6-Halogen substituted tetrazolopyridines exist in these conditions as mixtures of both forms, whereas in the case of 6, 8-disubstituted derivatives the equilibrium is strongly shifted towards the tetrazole form.

CONCLUSIONS

Halogen substituents exert a strong influence on the tetrazole–azide equilibrium in tetrazolo[1,5-*a*]pyridines. Depending on the position of substituents in the tetrazolopyridine ring they can stabilize or destabilize the tetrazole form. Especially clear is the influence of halogen atoms in position 5 because the higher the electronegativity of the atom the larger is it, with a tendency to open the tetrazole ring. The same substituents in position 8 stabilize only the tetrazole form. The presence of two halogen atoms in positions 6 and 8 facilitate opening of the bicyclic molecule in aprotic solvents. In TFA as the solvent the azide form is more preferred to the tetrazole form, although substituents in positions 8 or 6 and 8 stabilize the bicyclic structure. The IR spectra in the solid state and in solutions are of only qualitative significance, whereas NMR data are irreplaceable in the process of consideration of the tetrazole–azide tautomerization at the quantitative level. Based on ^{1}H NMR integrals, characterization of the influence of the nature and position of the halogen atoms becomes possible. The differences in ^{1}H, ^{13}C and ^{15}N spectral parameters (chemical shifts, coupling constants, longitudinal relaxation times) are the basis for distinguishing the tetrazole and azido forms in equilibrium. Calculated *ab initio* ^{13}C and ^{15}N absolute shieldings are very useful in signal assignments, whereas total SCF energies and charge distributions are of great importance in considerations of tetrazole–azide tautomerism.

Acknowledgements

Support for this work was partially provided by a grant from the Polish State Committee for Scientific Research, No. 3 T09A 010 12. We thank the Interdisciplinary Science Centre (ICM) of Warsaw University for computing time and providing programs. We also thank Dr J. W. Wiench for performing calculations.

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