EQUILIBRIUM CH ACIDITY OF ACETYLENIC DERIVATIVES OF N-ALKYLAZOLES IN DMSO

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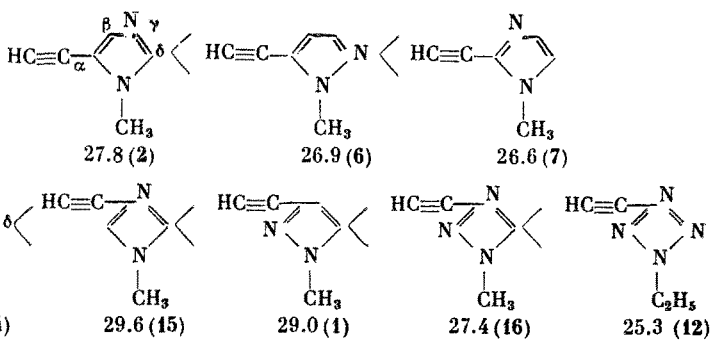
The equilibrium CH acidity of a group of ethynylazoles in DMSO was measured by an intermetallization method. The dependence of the acidity of these compounds on the structure of the heterocycle, position of the ethynyl group, and nature of the substituents has been examined.

Keywords: *ethylene-N-alkylazoles, equilibrium CH acidity, synthesis.*

There are few quantitative data on the CH acidity of terminal acetylenes [1]. Continuing investigations of the equilibrium CH acidity of aromatic and heteroaromatic acetylenes [2, 3], we determined the acidity of a new group of ethynylazoles in DMSO.

Table 1 presents the pK values of these compounds, obtained by an intermetallization method [4]. All the ethynyl-N-alkylazoles can be arbitrarily divided into two groups, depending on the position of the acetylenic substituent relative to the "pyrrole" nitrogen atom:



As it follows from a comparison of the pK value, the acidity of α-ethynylazoles increases depending on the position of the "pyridine" nitrogen atom in the ring: $\gamma < \delta < \beta$. The pattern of variation of the acidity for β-ethynylazoles noted earlier [2] was additionally confirmed by measurement and inclusion of pK of compound **1** into this series: $\delta < \gamma < \alpha$.

At a fixed position of the "pyridine" nitrogen atom in the ring, α-ethynylazoles have higher CH acidity than β-ethynylazoles. The "pyrrole" nitrogen atom increases the acidity of the ethynyl group (EG) in the adjacent position to an appreciably greater degree than the "pyridine" nitrogen atom (compare **15** and **2**, **1** and **6**). As was predicted on the basis of quantum chemical calculations [5], 1-methyl-2-ethynylimidazole (**7**), in which the EG experiences the simultaneous influence of the neighboring nitrogen groups of both types, proved to be the strongest acid among the ethynyldiazoles.

The acidity of ethynylazoles increases significantly with increasing total number of nitrogen atoms in the heterocycles, and in accordance with this, ethynyltetrazole (**12**) has the lowest pK value.

The observable values of the CH acidity of ethynylpyrazoles and -imidazoles are linear functions of the energies of stripping of a proton from the EG in each series, calculated by the CNDO-2 method in [5] (Fig. 1).

It is noteworthy that the acidity of the EG in various positions of the diazole ring corresponds to the reactivity of the same positions of unsubstituted diazoles, i.e., not containing EG. Thus, the reactivity of the CH component of the pyrazole ring increases in electrophilic substitution reactions in the sequence **4** > **3** > **5**, and the mobility of the proton of the EG in ethynylpyrazoles (**14**, **1**, and **6**) also increases. The order of variation of the pK values in ethynylimidazoles also agrees with the activity of the CH components of the imidazole ring with respect to electrophilic agents: **4** > **5** < **2** (**15**, **2**, and **7**).

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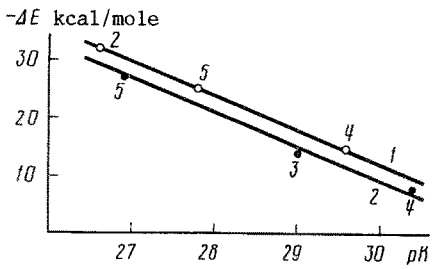


Fig. 1

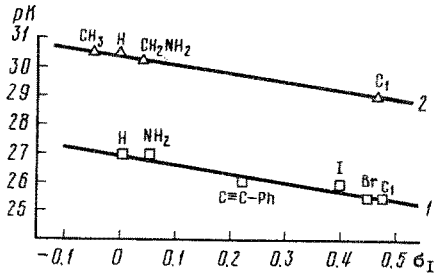


Fig. 2

Fig. 1. Dependence of pK of ethynyl-N-methyldiazoles on the energy of stripping of a proton in them: ΔE is the difference of the energy of stripping of a proton in acetylene HC≡CH and HetC≡CH; 1) position of the EG in N-methylimidazole; 2) position in N-methylpyrazole.

Fig. 2. Dependence of pK of ethynyl-N-methylpyrazoles on the substituents [6]: 1) for 4-substituted 1,3-dimethyl-5-ethynylpyrazoles; 2) for 5-substituted 1,3-dimethyl-4-ethynylpyrazoles.

TABLE 1. Equilibrium CH Acidity (pK) of Ethynyl-N-methylazoles and Equilibrium Constant of Intermetallization (K_{eq}) in DMSO

Compound	pK	Indicator* (pK)	K_{eq} †	Literature reference
1	29.0	PX (28.3)	0.21±0.01	[10]
2	27.8	»	3.0±0.1	[11]
3	27.6	»	4.7±0.2	[12]
4	27.0	»	19.6±0.1	
5	27.0	»	19.2±0.1	
6	26.9	TPP (26.2)	0.22±0.02	[10]
7	26.6	»	0.38±0.01	[13]
8	26.1	»	1.2±0.2	
9	26.0	»	1.6±0.4	
10	25.5	»	5.2±0.2	
11	25.5	»	5.0±0.2	
12	25.3	»	7.8±0.3	[14]
13	24-26	PF (18.5), TBF (24.6), PX	-	[15]

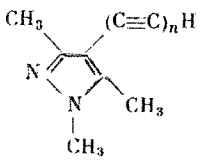
*PX) 9-phenylxanthene; TPP) 1,1,3,3-tetraphenylpropene; PF) 9-phenylfluorene; TBF) 9-*tert*-butylfluorene.

†Average of 5-6 measurements.

In a series of 4-substituted 1,3-dimethyl-5-ethynylpyrazoles, a correlation was detected between the acidity and the σ_i constants of the substituents (Fig. 2) (for the —C≡C—Ph group the value of σ_i was calculated from the function $\sigma_i = \sigma^*/6.23$, where $\sigma^* = 1.35$ [6]). An analogous dependence of pK on σ_i is realized in the series of 5-substituted 1,3-dimethyl-4-ethynylpyrazoles (Fig. 2, cf. [2]).

This means that conjugation of the heterocycle with the triple bond has no appreciable influence on the acidity of vicinal-substituted ethynylpyrazoles. Evidently it is reasonable to assume that the influence of the substituent in the compounds under consideration is exerted chiefly through the field effect, which predominates both over the effect of conjugation and over the "intrinsically" inductive effect transmitted along the bonds (the reaction site and substituent are separated by four bonds).

There are no data in the literature on the CH acidity of monosubstituted 1,3-diynes. We succeeded in estimating the acidity of 4-butadiynyl-1,3,5-trimethylpyrazole (**13**). It proved to be 5-7 orders of magnitude higher than in the corresponding ethynyl derivative (**13a**), which agrees with the data on the relative reactivity of terminal mono- and diacetylenes (for example, [7]):



(**13**), $n = 2$, pK = 24—26

(**13a**), $n = 1$, pK = 30.7 [2].

TABLE 2. Ethynylpyrazoles

Compound	Yield, %	Mp, °C (hexane)	Empirical formula	Found/Calculated, %			IR spectrum, ν, cm^{-1} (CCl_4)		PMR spectrum, δ, ppm ($CDCl_3$)			
				C	H	N	C≡C	≡C–H	N–CH_3	3-CH_3	C–H	others
4	46.5	56–57	$C_7H_8N_2$	69.71 / 69.67	6.65 / 6.71	23.11 / 23.31	2114	3311	3.80	2.17	3.38	6.14 (4-H)
5	84.5	121–122 (Benzene–petroleum ether)	$C_7H_9N_3$	62.14 / 62.20	6.78 / 6.71	31.06 / 31.09	2108	3306	3.73	2.09	3.65	2.90 (NH_2)
8	65	89–90	$C_{15}H_{12}N_2$	77.66 / 77.67	6.67 / 6.52	9.99 / 10.06	2122, 2219	3314	3.86	2.32	3.66	7.3–7.5 (Ph)
9	82	125–126 Dec.	$C_7H_7JN_2$	34.18 / 34.17	2.96 / 2.87	*	2119	3316	3.88	2.18	3.61	–
10	47.5	99–100 Dec.	$C_7H_7BrN_2$	42.33 / 42.24	3.58 / 3.54	†	2125	3313	3.84	2.18	3.63	–
11	66	74–75	$C_7H_7ClN_2$	53.88 / 54.38	4.55 / 4.56	‡	2127	3312	3.81	2.17	3.65	–

Found/Calculated, %:

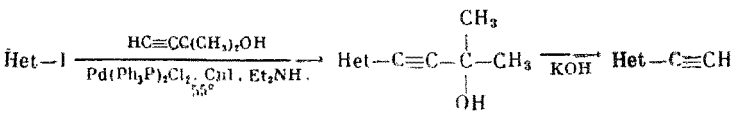
*I 51.59/51.58.

†Br 40.14/40.14.

‡Cl 23.05/22.93.

The pK of compound **13** could not be precisely measured as a result of side processes involving the diacetylenide anion, which complicates the monitoring of intermetallization reactions.

Most of the hetarylacetylenes presented in Table 1 were synthesized by catalytic condensation [8] of N-methyliodoazoles and dimethylethynylcarbinol, followed by cleavage of the tertiary acetylenic alcohols according to a reverse Favorsky reaction [9]:



EXPERIMENTAL

The equilibrium constants of the intermetallization reaction were determined spectrophotometrically on an SF-4A instrument using seamless vacuum apparatus and thoroughly purified DMSO according to the procedure for pK measurements described in [4]. The compounds were purified for the pK measurement by chromatography, recrystallization, and sublimation or fractional distillation under vacuum. The PMR spectra were recorded on a Varian XL-200 spectrometer, the IR spectra on a UR-20 instrument.

4-Bromo-5-iodo-1,3-dimethylpyrazole (17). To 8.9 g of 1,3-dimethyl-5-iodopyrazole (**16**) in 5 ml of AcOH was added 8 g of AcONa in 30 ml of H_2O and added 6.4 g Br_2 in 5 ml of AcOH dropwise at 20°C, exposed for 20 min, and neutralized the mixture with an aqueous solution of Na_2CO_3. The product was extracted with $CHCl_3$ (4 × 75 ml), filtered through Al_2O_3, the solvent distilled off, and the residue recrystallized from hexane. Yield 11.2 g (93%) (**17**), mp 129-130°C. Found, %: C 20.07, H 1.83, Br 26.31, I 41.27. $C_5H_6BrIN_2$. Calculated, %: C 19.96, H 2.01, Br 26.55, I 42.17. PMR spectrum ($CDCl_3$, δ, ppm): 2.24 (3-CH_3), 3.88 (N—CH_3).

1,3-Dimethyl-5-(3-methyl-3-hydroxybutyn-1-yl)-4-chloropyrazole (18). A 4.5 g portion of 5-iodo-1,3-dimethyl-4-chloropyrazole (**17**), 2.2 g of dimethylethynylcarbinol, 70 mg $Pd(PPh_3)_2Cl_2$, and 35 mg CuI in 50 ml of Et_2NH were mixed under Ar at 52-55°C for 12 h, diluted with 500 ml of ether, filtered, and the solvent distilled off. Chromatography on Al_2O_3 (II degree, 80 × 120 mm), followed by crystallization from hexane, yielded 3.0 g (76%) (**18**), mp 41-42°C. Found, %: C 56.45, H 6.11, Cl 16.68. $C_{10}H_{13}ClN_2O$. Calculated, %: C 56.47, H 6.16, Cl 16.67. PMR spectrum ($CDCl_3$, δ, ppm): 1.54 [$C(CH_3)_2$]; 2.12 (3-CH_3); 3.70 (N—CH_3), 3.78 (OH). IR spectrum ($CHCl_3$, ν, cm^{-1}): 2237 (C≡C), 3605 (OH).

1,3-Dimethyl-5-(3-methyl-3-hydroxybutyn-1-yl)-4-phenylethynylpyrazole (19). Produced from 4-iodo-1,3-dimethyl-5-(3-methyl-3-hydroxybutyn-1-yl)pyrazole (**17**) with phenylacetylene under analogous conditions; reaction time 14 h, yield of (**19**) 65%, mp 89-90°C. Found, %: C 77.69, H 6.47, N 9.99. $C_{18}H_{18}N_2O$. Calculated, %: C 77.67, H 6.52, N 10.06. PMR spectrum ($CDCl_3$, δ, ppm): 1.61 [$C(CH_3)_2$]; 2.29 (3-CH_3); 2.72 (OH); 3.80 (N—CH_3). IR spectrum ($CHCl_3$, ν, cm^{-1}): 2216 (C≡C), 3610 (OH).

The same method was used to synthesize 4-bromo-1,3-dimethyl-5-(3-methyl-3-hydroxybutyn-1-yl)pyrazole (**20**) and 4-amino-1,3-dimethyl-5-(3-methyl-3-hydroxybutyn-1-yl)pyrazole (**21**) from **17** and 4-amino-1,3-dimethyl-5-iodopyrazole (**16**), respectively. Compounds **20** and **21** were introduced into an alkaline cleavage reaction without additional purification.

1,3-Dimethyl-5-ethynylpyrazole (4). A 1.4 g portion of 1,3-dimethyl-5-(3-methyl-3-hydroxybutyn-1-yl)pyrazole (**17**) and 0.14 g of powdered KOH in 3 ml of Alkaren high-vacuum oil were heated in an apparatus for vacuum sublimation at 100-105°C (1 mm Hg), whereupon 0.6 g of **4** sublimed. Chromatography on Al_2O_3 (II degree, 50 × 120 mm), followed by sublimation and crystallization from hexane, yielded 0.45 g of **4** (46.5%).

The remaining ethynylpyrazoles were produced analogously; the yields and constants are presented in Table 2.

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