Reactions of Azolium Cations. II [1]. Regioselective N2 Alkylation of 5-Aryltetrazoles with Isopropyl Alcohol in Sulfuric Acid Media: Effect of Electronic Properties of Aryl Substituents on the Reaction Rate

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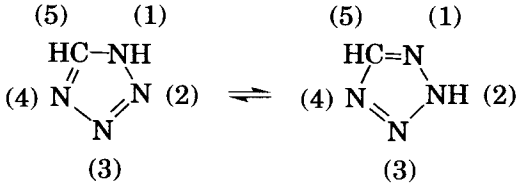
Abstract

Kinetics of regioselective N2 alkylation of a series of 5-(R-phenyl)tetrazoles with isopropyl alcohol has been studied in 88.2, 94.3, and 98.3% (w/w) sulfuric acid at 25°. The true rate constants were evaluated, logarithms of which were found to correlate with σ° constants of phenyl substituents as $\log k = -0.488\ \sigma^\circ - 0.417$. Small value of Hammett constant ρ is evidence of a considerable isolation of the reaction center from the influence of the substituent at position C5 of the heteroring. This conclusion is confirmed by results of MNDO quantum chemical calculations of a series of 5-substituted tetrazolium cations. A correlation between logarithms of the true rate constants and the calculated net effective charges on atoms N2(N3) for 5-(R-phenyl)tetrazolium cations has been revealed. © 1995 John Wiley & Sons, Inc.

Introduction

Tetrazole is five-membered NH-heterocycle with four nitrogen atoms in the ring, numbered as shown in Scheme I:



Scheme I

Its derivatives possess many interesting features and find rather wide application in various fields of medicine [2], technology, agriculture, etc. [3].

Alkylation of NH-tetrazoles is the most common and convenient (and often the only) route to their N-alkyl derivatives; however, it is still far from being completely understood [4]. Tetrazoles can be alkylated either at a N1 or N2 position, and usually both isomeric alkylation products are obtained [3,4]. Their ratio depends on many factors, and mainly on electronic and spatial properties of substituent at C5 [4].

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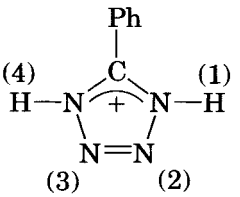
As shown recently, alkylation of 5-monosubstituted tetrazoles with secondary and tertiary aliphatic alcohols in a concentrated sulfuric acid medium results in the formation of the corresponding 2-alkyl derivatives only, independent of the nature of the 5-substituent in the heteroring [5]. Investigation on kinetics of the alkylation of 5-phenyltetrazole with isopropyl alcohol [1] has shown the reacting particles in this reaction to be 1H, 4H-5-phenyltetrazolium cation (i.e., protonated at N4 position 5-phenyltetrazole) and isopropyl cation generated from the protonated alcohol. The interaction of these particles (TH_2^+ and R^+, respectively, Scheme II) occurs at the rate-limiting stage and leads to the formation of a twice positively charged unstable intermediate (TH_2R^{++}). Deprotonation of the latter at the second, kinetically uncontrolled, stage yields protonated 2-isopropyl-5-phenyltetrazole (THR^+):

$$TH_2^+ + R^+ \xrightarrow[\text{slow}]{k} TH_2R^{++} \xrightarrow[\text{fast}]{} THR^+ + H^+$$

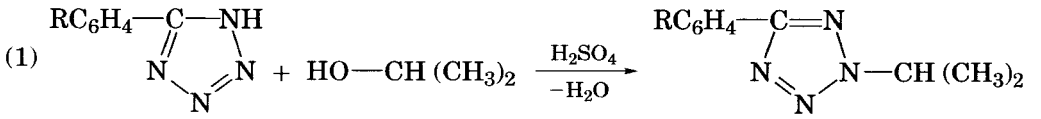
Scheme II

The regioselectivity is caused by the circumstance, that only N2 position (or N3, which is identical due to symmetricity) is accessible in the alkylation substratum, whereas alternative reaction centers, nitrogens N1 and N4, are blocked by the attached protons (Scheme III):



Scheme III

To gain deeper insight into the mechanism of this interesting process, influence of the electronic properties of the substituent R in the phenyl ring upon the reactivity of 5-(R-phenyl)tetrazoles in the reaction of their regioselective N2 alkylation with isopropyl alcohol in the aqueous sulfuric acid solutions was investigated:



1a–f 2a–f

R = *p*–Me (a); H (b); *p*–Cl (c); *m*–Br (d); *m*–NO_2 (e); *p*–NO_2 (f)

Experimental

The 5-aryltetrazoles were prepared and purified by the known methods: 5-phenyltetrazole [6]; 5-*p*-tolyltetrazole [7]; 5-*p*-chlorophenyltetrazole and 5-*m*-bromophenyltetrazole [8]; and 5-*m*-nitrophenyltetrazole and 5-*p*-nitrophenyltetrazole [9].

Isopropyl alcohol was purified for kinetic experiments in accordance with ref. [10].

2-Isopropyl-5-phenyltetrazole has been characterized formerly [1]. The other 2-isopropyl-5-aryltetrazoles were prepared by the method analogous to that reported in ref. [5]. Compounds 2a, c, and d were purified by repeated distillation in vacuo and solids 2e and f were recrystallized from ethanol-water mixtures. Characteristics of the synthesized tetrazoles are as follows: 2-isopropyl-5-*p*-tolyltetrazole (2a), b.p. 90°/0.03 mm Hg, n_D^{20} 1.5427; 2-isopropyl-5-*p*-chlorophenyltetrazole (2c), b.p. 92° /0.02 mm Hg, n_D^{20} 1.5548; 2-isopropyl-5-*m*-bromophenyltetrazole (2d), b.p. 111° /0.02 mm Hg, n_D^{20} 1.5703; 2-isopropyl-5-*m*-nitrophenyltetrazole (2e), m.p. 74°; and 2-isopropyl-5-*p*-nitrophenyltetrazole (2f), m.p. 82°.

Kinetics of the alkylation of tetrazoles 1a–f was studied in 88.2, 94.3, and 98.3% (w/w) sulfuric acid at 25.0 ± 0.1°C. The medium acidity ensured the tetrazoles to be fully protonated at N4 position of the heteroring in all experiments. UV spectrophotometric technique was used for kinetic investigations, since UV spectra of the 5-aryltetrazoles and these of their 2-isopropyl derivatives appear to differ significantly in sulfuric acid of the above-mentioned concentrations (Table I). The pseudo-first-order reaction conditions ([tetrazole]<<[alcohol]) were used in all kinetic experiments, which were carried out as reported previously [1].

Values of the true rate constants were calculated with the use of the equation derived in our previous work [1]:

$$k = k_{obs}(1 + 1/I_t)(1 + a_w K_{R^+}(1 + 1/I_a)), \quad (2)$$

where k_{obs} is observed second-order rate constant; I_t and I_a are ionization ratios of the corresponding 5-aryltetrazole and isopropyl alcohol, respectively; $K_{R^+} = -5.30$ [1] is the equilibrium constant of isopropyl cation formation from protonated isopropyl alcohol; and a_w is water activity.

In practice, we neglected the term $1/I_t$ in eq. (2), since even for the least basic tetrazole 1f ($pK_{BH^+} = -3.88$ [11]) in the least acidic medium (88.2% H_2SO_4) $1/I_t$ value is about 10^{-5}. The ionization ratios I_a were calculated by Cox–Yates method [12] with parameters $pK_{BH^+} = -2.02$ and $m^* = 0.18$ [13].

Quantum chemical calculations of 5-substituted tetrazolium cations with full optimization of the structures were performed by MNDO method [14], which is shown to be the most suitable for tetrazole derivatives [15], using QCPE program No. 353.

TABLE I. UV Spectra of 5-aryl- and 2-isopropyl-5-aryltetrazoles in 94.3% sulfuric acid at 25°.

Compound	λ_{max}, nm	ϵ_{max}, L mol^{-1} cm^{-1}
1a	269	17500
2a	257	14700
1b	255	15400
2b	243	13400
1c	269	18300
2c	259	17700
1d	257	11700
2d	245	12800
1e	239	19700
2e	233	20400
1f	271	14500
2f	278	13900

Results and Discussion

As for 5-phenyltetrazole [1], reaction (1) was ascertained to be the first-ordered on all of the 5-aryltetrazoles (1a–f), and second-ordered overall. Semilogarithmic anamorphoses of the kinetic curves were linear up to high conversion extents (above 80%) in all experiments. The initial concentrations of the 5-aryltetrazoles were practically equal to these obtained by the extrapolation of the anamorphoses to the moment of the reaction start. The observed second-order rate constants k_{obs}, estimated from both the diminution of the initial tetrazoles 1a–f and the accumulation of the corresponding final products 2a–f, are in good agreement, also (Table II), which points out the absence of accumulation of any intermediate products during reaction (1).

As seen from Table II, the rate of the alkylation decreases regularly when strengthening electron withdrawing properties of a substituent in a phenyl ring. Logarithms of the true rate constants k are found to correlate with σ° constants of the substituents:

$$\log k = -(0.488 \pm 0.002)\sigma^\circ - (0.417 \pm 0.001), \quad (3)$$

correlation coefficient $r = 0.999$, and number of points $n = 6$. Negative value of Hammett ρ constant, -0.488, confirms the reaction to be electrophilic in regard to the heterocycle, whereas relatively small ρ magnitude points out low sensitivity of the reactivity of protonated 5-aryltetrazoles to the alteration of nature of the aryl substituent. It means that the reaction center of the tetrazole cycle is isolated from the influence of the 5-substituent to a considerable extent. Obviously, such sites are atoms N2 and N3 (cf., Scheme III).

The proposed mechanism, assuming interaction of two cations, might seem unusual at first sight. However the results of MNDO quantum chemical calculations of such particles do not contradict the possibility of the reaction under consideration. Indeed, isopropyl cation is a strong electrophile, a substantial positive charge of +0.432 being concentrated on its central carbon atom [16]. Calculated charge distribution in the tetrazole cycle of 5-substituted tetrazolium cations is given in Table III. These data show that in a symmetrical tetrazolium cation (cf., Scheme III) positive charge is mainly localized on carbon atom of the heterocycle, and appreciable electron density

TABLE II. Observed second-order rate constants and true rate constants (both in L mol^{-1} s^{-1}) of alkylation of 5-aryltetrazoles with isopropyl alcohol in aqueous sulfuric acid solutions at 25°.

Compound	Analytical wavelength, nm	$k_{obs}10^3$ (k) at concentration of H_2SO_4, %			$-\log k$[a]
		88.2	94.3	98.3	
1a	275[b]	3.57 (0.425)	33.2 (0.497)	142 (0.425)	0.343
	245[c]	3.59 (0.428)	33.2 (0.497)	150 (0.449)	
1b	260[b]	3.04 (0.362)	28.0 (0.419)	125 (0.374)	0.417
	235[c]	2.98 (0.355)	28.1 (0.421)	123 (0.368)	
1c	280[b]	2.21 (0.263)	21.0 (0.314)	89.9 (0.269)	0.548
	245[c]	2.20 (0.262)	20.6 (0.308)	93.6 (0.280)	
1d	265[b]	1.91 (0.227)	18.1 (0.271)	77.3 (0.232)	0.606
	240[c]	2.00 (0.238)	18.3 (0.274)	81.3 (0.244)	
1e	225[c]	1.40 (0.167)	12.9 (0.193)	54.9 (0.164)	0.758
1f	260[b]	1.17 (0.139)	11.1 (0.166)	50.0 (0.150)	0.817
	295[c]	1.20 (0.143)	11.1 (0.166)	50.0 (0.150)	

[a] For k as arithmetical means of the values calculated for three specified concentrations of sulfuric acid.
[b] Wavelength for monitoring the diminution of an initial 5-aryltetrazole.
[c] Wavelength for monitoring the accumulation of the corresponding 2-isopropyl-5-aryltetrazole.

TABLE III. Charge distribution in the tetrazole cycle of 1H, 4H-5-R-tetrazolium cations as calculated by MNDO method.

R	Net effective charge on atom		
	N1 (N4)	N2 (N3)	C
p-MePh	−0.19174	+0.08313	+0.34909
Ph	−0.18949	+0.08400	+0.34767
p-ClPh	−0.18577	+0.08625	+0.34424
m-NO_2Ph	−0.17623 (−0.17585[a])	+0.09045 (+0.09136[a])	+0.33347
p-NO_2Ph	−0.17484	+0.09131	+0.33102
Me	−0.17095	+0.09494	+0.24461
H	−0.16940	+0.09924	+0.26859
Cl	−0.15339	+0.10505	+0.24357
CF_3	−0.11767	+0.11192	+0.12600
NO_2	−0.11510	+0.11174	+0.16801

[a] Data for the atom nearer to the *m*-substituent in phenyl ring.

is left on equivalent atoms N2 (N3). The latter very slightly depends on the nature of the 5-substituent, and with that the above-stated weak dependence of the reactivity of 5-aryltetrazoles on the nature of the aryl substituent becomes understandable. It is noteworthy that logarithms of the true rate constants for reaction (1) correlate with the calculated net effective charges (q) on atoms N2 (N3) of the corresponding 5-aryltetrazolium cations:

$$\log k = -(55.735 \pm 1.998)\,q + (4.274 \pm 0.174), \tag{4}$$

correlation coefficient $r = 0.998$, and number of points $n = 5$.

This dependence provides an opportunity to get some idea about rate of regioselective N2 alkylation with isopropyl alcohol for other tetrazoles: values of k amount ca. 0.1 L mol^{-1} s^{-1} for 5-methyltetrazole to ca. 0.01 L mol^{-1} s^{-1} for 5-trifluoromethyl derivative.

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