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Kinetics and Mechanism of Izomerization of *N*-Alkoxycarbonyl-5-aroxytetrazoles*

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Abstract—The kinetics and mechanism of the N^2–N^1-isomerization of 2-methoxycarbonyl-5-(*p*-X-phenoxy)-tetrazoles (X = H, CH_3, $NHCOCH_3$, Cl, Br, NO_2) were studied by ^{1}H NMR spectroscopy in a DMSO-d_6–$CDCl_3$ mixture (25 : 75). The rate of isomerization of the N^2-isomer into N^1-isomer fit the first-order equation (after three half-conversion periods). The isomerization is accompanied by hydrolysis and decarboxylation. The Hammett plot of $\ln(k_X/k_H)$ for the isomerization showed a good correlation with σ^- values (ρ^- = 1.33, r = 0.965). A poor correlation with σ values was obtained. The kinetic data, the effect of solvent polarity, the substituent effects, and the results of AM1 quantum-chemical calculations suggest an ionic mechanism of the isomerization in polar solvents and a concerted mechanism in nonpolar solvents.

Tetrazoles constitute a class of compounds which are very important for medical chemistry. Substituted tetrazoles were found to exhibit a wide spectrum of neurological activity which, depending on the substitution pattern, ranges from strong stimulation of the nervous system to depressive action. Tetrazolecarboxylic acids are widely used as pharmacophores in drug design, specifically, for creation of anticancer, antimicrobial, antihypertensive, and antiallergic agents. Tetrazole derivatives have recently attracted increasing attention due to their industrial applications. It is quite probable that pharmacological activity of tetrazoles is related to their physicochemical properties, so that thorough investigations in the field of tetrazole derivatives were initiated many years ago [1–5]. Every year numerous publications appear on the chemical behavior of tetrazoles, in particular on their prototropic tautomerism [6–15] and izomerizations [16]. Analogous ready isomerizations have been reported for a few other azoles having a substituent on the nitrogen, e.g., for benzotriazole [10], benzimidazole [17], and pyrazole derivatives [18].

The main difficulty in the studies of tetrazole compounds is that 1-tetrazole, 2-tetrazole, and the corresponding open-chain form of 1-tetrazole in solution can form an equilibrium mixture whose composition depends on the substitution pattern, solvent polarity, and other factors. Generally, each isomer has its own specific chemical and pharmacological properties. For example, some 1,5-disubstituted tetrazoles exhibit a strong stimulating activity on the central nervous system while 2,5-disubstituted analogs do not [19]. On the other hand, most azides (which are important precursors of such compounds as amines, aziridines, isoureas, oxadiazoles, and many others) are carcinogenic [14, 15, 20]. Therefore, the major and the most important task is to control the isomerization process. It is also important to find conditions ensuring displacement of the equilibrium between isomers toward the desired species. These goals could be achieved through understanding of the isomerization mechanism.

Katritzky *et al*. studied the kinetics of interconversions of *N*-(α-aminoalkyl)benzotriazoles and found that the reaction follows a dissociation–recombination pattern. The same authors also found that tetrazoles undergo fast isomerization involving N^1–N^2-migration of the substituent [10] due to activation of the C–N bond toward cleavage. This tendency was advantageously utilized in many synthetic transformations, including reactions with nucleophiles [21–26].

Dabbagh and Lwowski (see [16] and references therein) studied the equilibria of 5-substituted 1- and 2-tetrazoles, the substituent at C^5 remaining nearly unchanged, and showed that 1- and 2-alkoxycarbonyltetrazoles and, in some cases, imidoyl azides occur in equilibrium. However, in the srystalline state only one isomer always prevails, depending on the substituent

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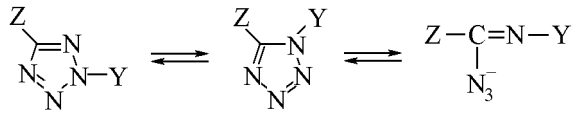
Table 1. Substituent and solvent effects on the position of the equilibrium between 1,5- and 2,5-disubstituted tetrazoles at room temperature[a] [16]



2-Y-Tetrazol 1-Y-Tetrazol Azid

Substituents		Isomer fraction,[b] %		
Z	Y	2-tetrazole	1-tetrazole	azide
CH_3O	CO_2CH_3	62	38	0
CH_3O[c]	CO_2CH_3	100	0	0
CH_3O	$CO_2CH_2CCl_3$	46	37	17
CH_3O[c]	SO_2CF_3	0	0	100

[a] In $CDCl_3$ unless otherwise stated.

[b] Calculated from the ^1H NMR spectra.

[c] In diethyl ether.

concentration and solvent polarity. The authors came to x_{the} following conclusions:

(1) Metoxycarbonyl-5-alkoxy(aroxy)tetrazoles and related imidoyl azides do exist as an equilibrium mixture;

(2) The position of the equilibrium depends upon the electronic nature of the N-substituent, concentration, and solvent polarity;

(3) In nonpolar solvents weak electron-withdrawing groups (such as CO_2CH_3) favor acylation of 5-substituted tetrazoles at the *2*-position;

(4) Moderate electron-withdrawing groups (such as $CO_2CH_2CCl_3$ and CO_2CCl_3) favor displacement of the equilibrium toward 1-alkoxycarbonyl isomers;

(5) Strong electron-acceptor groups (CN, SO_2CH_3, SO_2CF_3) favor formation of the azide structure;

(6) The rate of isomerization of both tetrazoles and open-chain azide isomers increases as their concentration and solvent polarity rise;

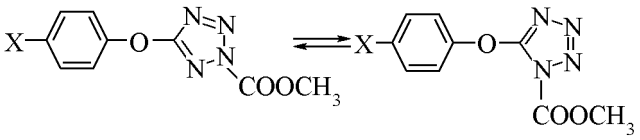
(7) In the solid phase or less polar solvents (e.g., in diethyl ether), only one of the three isomers is formed, depending on the nature of substituent in position *1* or *2*;

(8) The ^1H NMR spectra of 1(2)-methoxycarbonyl-5-methoxytetrazoles, recorded immediately after addition of a base, indicate that initially 1-substituted isomer is formed; it then gives rise to an equilibrium mixture with the 2-isomer and/or imidoyl azide;

(9) Crystallization of the equilibrium mixture of 1- and 2-methoxycarbonyl-5-methoxy(or ethoxy)tetrazoles from diethyl ether gives pure 2-substituted tetrazole.

The aim of this work was to gain a better understanding of the mechanism of isomerization of N-substituted tetrazoles. First, we studied the effect of the 5-substituent (keeping the substitution at the 1- or 2-position constant) and solvent polarity on the rate of N^1–N^2-isomerization of N-alkoxycarbonyl-5-aroxytetrazoles (and possibly of the azide isomers) at room temperature (Scheme 1). The following solvents were examined: CCl_4, $CDCl_3$, C_6D_5N, CD_3COCD_3, CD_3OD, CD_3CN, D_2O, and $CDCl_3$–DMSO-d_6 mixtures. Second, the rate constants for disappearance of 2-substituted tetrazoles were calculated and correlated with the Hammett substituent constants σ and σ^- [27]. Finally, we performed AM1 quantum-chemical calculations of the molecular geometry of the compounds under study. We tried to find evidences indicating that the isomerization of tetrazoles follows an ion pair mechanism and conditions to control the state of the equilibrium toward the desired species.

Scheme 1.



II, IV, VIII, X XII, XIV **I, III, VII, IX, XI, XIII**

I, **II**, X = CH_3, **III**, **IV**, X = H; **VII**, **VIII**, X = Cl; **IX**, **X**, X = Br; **XI**, **XII**, X = NHAc; **XIII**, **XIV**, X = NO_2.

Initially, we expected to observe a rapid isomerization (within hours) of 2-tetrazoles into 1-tetrazoles in chloroform, as reported previously [16]. However, we were surprised not to observe isomerization in nonpolar solvents (such as CCl_4 and $CHCl_3$) over several days. This fact prompted us to study the isomerization eqilibria of N-substituted tetrazoles in more detail.

Solvent effect. In a polar solvent, such as DMSO, the isomerization was very fast (in some cases the rate could not be measured, and the process was accompanied by hydrolysis and decarboxylation. The best solvent system ensuring a moderate rate of the isomerization and minimal contribution of side reactions was a mixture of $CDCl_3$ with DMSO-d_6 at a weight ratio of 75 : 25. In this solvent system all the examined 1-methoxycarbonyl-5-aroxytetrazoles were in equilibrium with the corresponding 2-isomer but

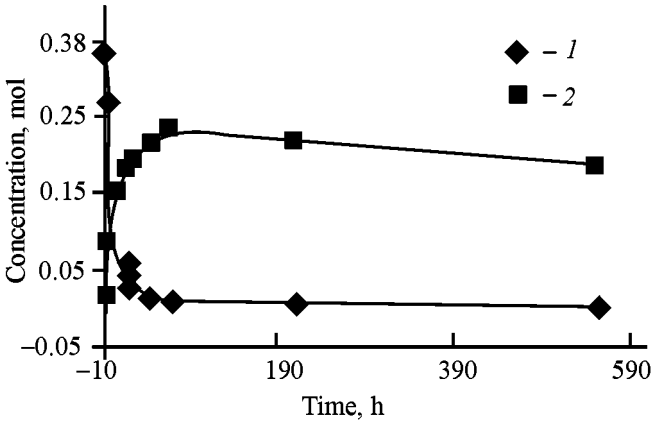


Fig. 1. Typical kinetic curves for the isomerization of (*1*) 2-methoxycarbonyl-5-(*p*-nitrophenoxy)tetrazole and (*2*) 1-methoxycarbonyl-5-(*p*-nitrophenoxy)tetrazole in $CDCl_3$–DMSO-d_6 (72 : 25, by weight) at room temperature.

not with the imidoyl azide. Figure 1 shows a typical kinetic curve for the isomerization of *N*-methoxycarbonyl-5-(*p*-nitrophenoxy)tetrazole. Here, hydrolysis and decarboxylation of the substrate (minor pathways) competed with its isomerization. The degree of isomerization and the contribution of side reactions (hydrolysis and decarboxylation) depend on the substituent nature and solvent polarity (Tables 2, 3). The data in Table 3 show the effect of solvent polarity on the isomerization rate and the extent of hydrolysis and decraboxylation of 2-methoxycarbonyl-5-(*p*-bromophenoxy)tetrazole. The contribution of the isomerization decreases and the contributions of hydrolysis and decarboxylation increase with rise in the solvent polarity.

Table 2. Transformations of 2-methoxycarbonyl-5-(*p*-X-phenoxy)tetrazoles in $CDCl_3$–DMSO-d_6 (75 : 25, by weight) at room temperature

Compd. no.	Time, h	Conversion,[a] %		
		hydrolysis	decarboxylation	izomerization
II	127.4	7.8	22.1	70.1
IV	123.1	5.3	13.2	81.5
VIII	127.2	10.7	20.2	69.1
X	126.9	8.1	14.7	77.2
XII	122.9	8.0	14.0	78.0
XIV	73.12	20.3	16.2	63.5

[a] Calculated from the ^{1}H NMR data.

Tetrazole (**X**) undergoes fast and complete (100%) hydrolysis on addition of D_2O to its solution in chloroform, prepared in an NMR ampule. The rate of solvolysis of **X** in less polar methanol was slow in favor of the isomerization. This is in good agreement with the ionic nature of intermediates whose dissociation is faster in more polar solvents. The rates of

Table 3. Effect of solvent polarity on the isomerization, hydrolysis , and decarboxylation of 2-methoxycarbonyl-5-(*p*-bromophenoxy)tetrazole (**X**) at room temperature

Solvent[a]	ε	Ratio **X** : **IX**	Isomerization, %	$k_{ap} \times 10^6$,[b] s^{-1}	Hydrolysis, %	Decarboxylation, %
$CDCl_3$ (120)[c]	4.7	–	–	–	–	–
Pyridine-d_5 (7.93)	12	0.13	34.25	206	34.24[d]	31.5
CD_3COCD_3[c]	21	–	–	–	–	–
CD_3OD (8.03)	33	0.15	55.29	63.3	32.94	11.8
CD_3CN[e]	36	2.5	12.5	Fast	40.5[d]	15.5
D_2O[e, f]	78.5	–	0	–	100	0
DMSO-d_6–$CDCl_3$ (w/w)						
100 : 0 (8.45)	49	0.55	41.1	221	36.8	22.1
75 : 25 (6.25)	–	0.78	46.0	120	34.0	20.0
50 : 50 (6.38)	–	1.0	64.8	103	19.0	16.2
25 : 75 (11.9)	–	3.2	88.7	5.61	7.1	4.2
22 : 78 (7.83)	–	3.4	91.5	5.58	5.1	3.4

[a] The numbers in parentheses denote the time (h) after which a sample was withdrawn for analysis.
[b] Isomerization rate constant [Eq. (1)].
[c] No conversion.
[d] Solvolysis.
[e] Instantaneous reaction.
[f] In chloroform shaken with D_2O.

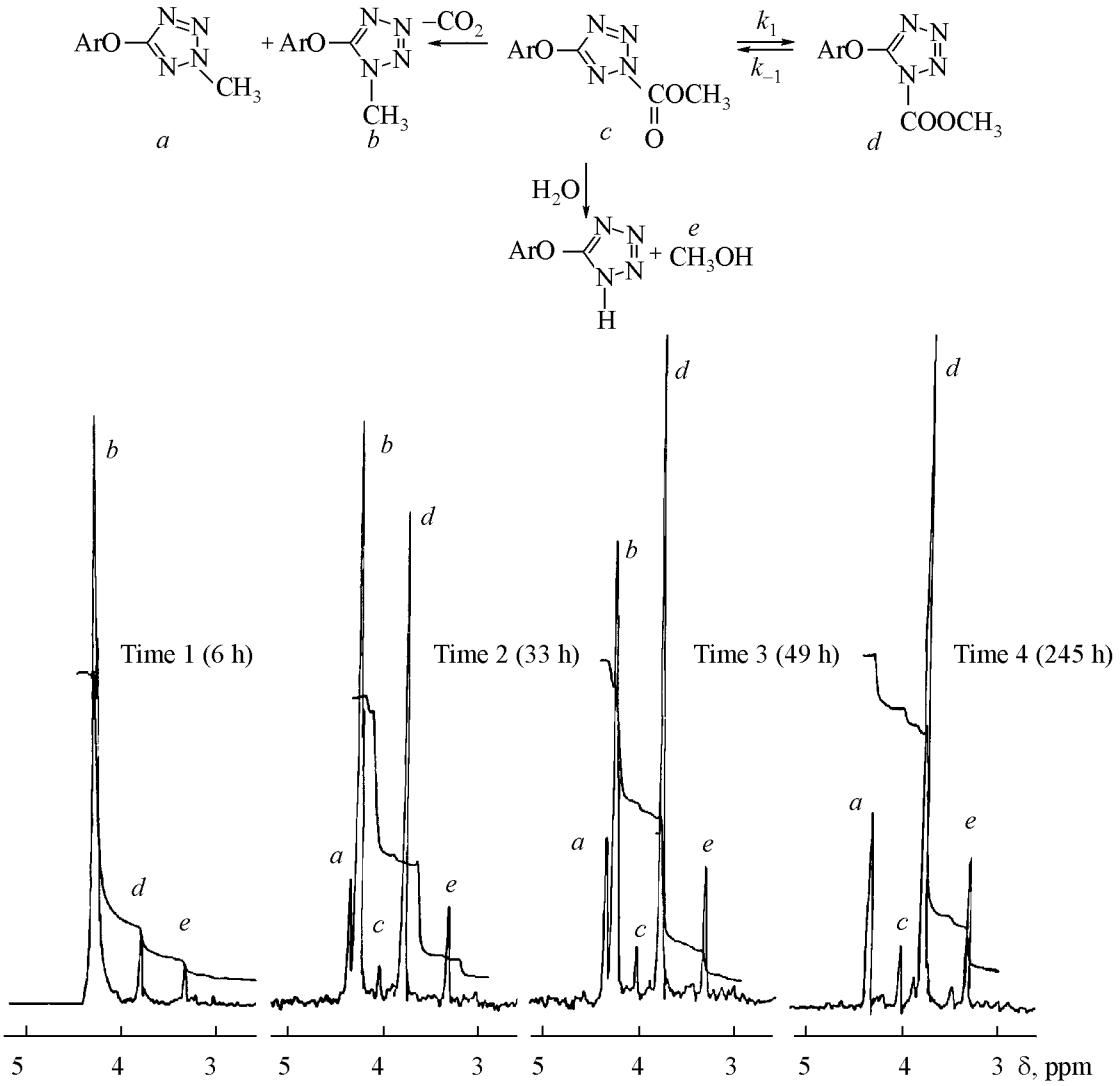


Fig. 2. Variation of the ^{1}H NMR spectrum in the course of transformation of 2-methoxycarbonyl-5-(*p*-chlorophenoxy)tetrazole **VIII** into equilibrium mixture of 1- and 2-tetrazoles and hydrolysis and decarboxylation products.

isomerization, hydrolysis, and decarboxylation of **X** in pyridine-d_5 were nearly the same. In acetonitrile-d_3, the rate of solvolysis was higher than the rates of the other competing processes. No isomerization was observed in chloroform and acetone-d_6 over several days (Tables 2, 3).

Figure 2 shows a typical portion of the ^{1}H NMR spectrum illustrating the disappearance of 2-methoxycarbonyl-5-(*p*-chlorophenoxy)tetrazole and appearance of 1-methoxycarbonyl-5-(*p*-chlorophenoxy)tetrazole. Protons of the methyl groups in N^2- and N^1-substituted isomers give signals at δ 4.30 and 3.80 ppm, respectively, i.e., the signal of the 2-isomer appears in a weaker field. The reason is that the N^2 atom is linked to two nitrogen atoms, whereas the N^1 atom in the 1-isomer is linked to nitrogen and carbon. The signal at δ 3.35 ppm belongs to methanol which is formed along the hydrolysis pathway (side reaction). Most probably, the hydrolysis is caused by traces of water absorbed by the solvent during relatively long period of kinetic measurements. The formation of methanol (which is also confirmed by IR spectra) in the equilibrium mixture is responsible for further solvolysis. The signals at δ 4.05 and 4.35 ppm belong to 1-methyl- and 2-methyl-5-(*p*-chlorophenoxy)tetrazoles, respectively, which are formed by thermal decarboxylation; 2-alkyltetrazoles are always the major isomers [27]. The decarboxylation is unusual at room temperature; generally, it requires much higher temperatures (350°C) [28] (Table 3).

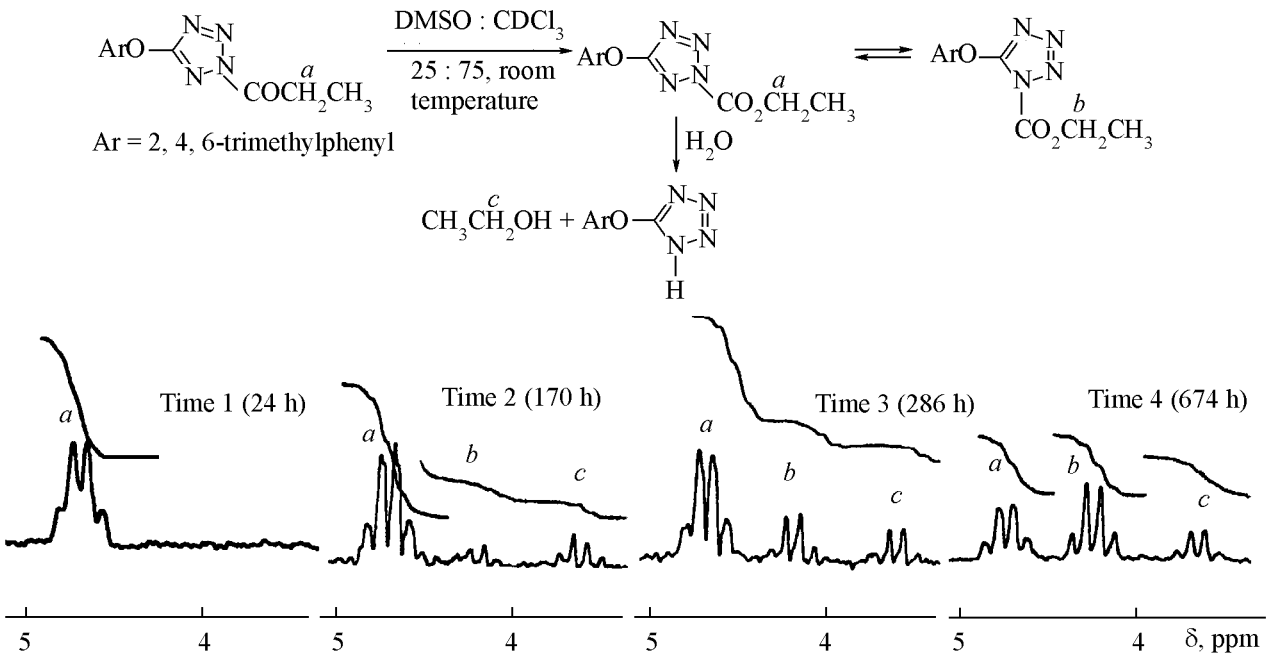


Fig. 3. Variation of the ^{1}H NMR spectrum in the course of transformation of 2-ethoxycarbonyl-5-mesityloxytetrazole (**XX**) into equilibrium mixture of 1- and 2-tetrazoles and hydrolysis products.

The IR spectra of the equilibrium mixture showed no azide band (methoxycarbonyl group is a relatively weak electron-withdrawing substituent, whereas only moderate to strong electron-withdrawing groups favor the formation of azide isomer; Table 1) [16]. The occurrence of isomerization is confirmed by the presence of hydroxy group absorption due to methanol and by the low-frequency shift of the carbonyl band of 2-methoxycarbonyltetrazole by about 50 cm^{-1}. The carbonyl absorption frequency shifts due to lower electronegativity of the N^1 nitrogen atom in the 1-isomer.

The rate of isomerization of 2-ethoxycarbonyl-5-mesityloxytetrazole (**XX**) (Fig. 3) is low, $k = 4.20 \times 10^{-7}$ s^{-1}. In this case the equilibrium does not shift completely toward the N^1-isomer over 674 h (cf. the data for the other tetrazoles, given in Tables 3 and 4 and Fig. 2).

Isomerization kinetics. The kinetics of the isomerization were studied by ^{1}H NMR spectroscopy.

Table 4. Kinetic parameters of the isomerization of 2-methoxycarbonyl-5-(*p*-X-phenoxy)tetrazoles in $CDCl_3$–DMSO-d_6 (75 : 25, by weight) at room temperature

Compound no.	N^2-to-N^1 isomer ratio	$[T_2]_{eq} \times 10^5$, Mn[a]	$\tau_{eq} \times 10^{-5}$, [b] s	$\tau_{1/2} \times 10^{-5}$, s	$k_{ap} \times 10^6$, [c] s^{-1}	r[d]
II	0.69	4.56	8.81	1.55	4.47 ($>3\tau_{1/2}$)	0.990
IV	0.38	2.27	10.3	1.71	4.05 ($>4\tau_{1/2}$)	0.993
VIII	0.20	0.52	4.58	1.34	5.17 ($>3\tau_{1/2}$)	0.998
X	0.14	0.45	8.65	1.24	5.61 ($>3\tau_{1/2}$)	0.994
XII	0.09	2.41	4.42	0.93	7.41 ($>3\tau_{1/2}$)	0.994
XIV	0.02	0.50	7.78	0.26	26.50 ($>4\tau_{1/2}$)	0.994

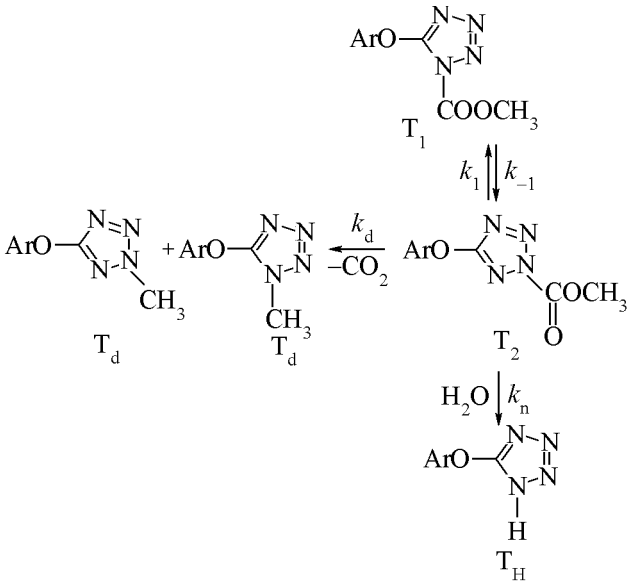
[a] Molal concentration.
[b] Equilibration period; after that time, the tetrazole concentrations in the mixture no longer changed to an appreciable extent.
[c] First-order rate constant for disappearance of the N^2-isomer, determined from the ^{1}H NMR data.
[d] Correlation coefficient.

The rate of disappearance of 2-methoxycarbonyl-5-(*p*-XC_6H_4O)tetrazoles (X = CH_3, H, Cl, Br, AcNH, NO_2) was measured in a $CDCl_3$–DMSO-d_6 mixture (75 : 25, by weight) (Tables 3, 4). The relative intensity of the methyl proton signal was normalized against the aromatic proton signals whose intensity did not change during the process. The rate of disappearance of the N^2-isomer conformed to the first-order kinetics [after 3–4 half-conversion periods; Scheme 2, Eq. (1)]. In all cases the equilibrium was displaced toward the more polar N^1-isomer (Scheme 2, Tables 2–4, Fig. 1).

The geometry of tetrazoles was optimized in terms of the AM1 semiempirical approximation (Table 5). The calculation results showed that more polar N^1-tetrazoles are more stable than their N^2-isomers (except for compound **XIII**). These findings are consistent with the shift of the equilibrium toward the N^1-isomer in $CDCl_3$–DMSO-d_6 (75 : 25).

Substituent effects. Figure 4 shows the Hammett plot of $\ln(k_X/k_H)$ versus substituents constants σ^- [12] for the N^2–N^1-isomerization of 2,5-disubstituted tetrazoles; a good correlation is observed, $\rho^- = 1.33$, $r = 0.965$. However, a poor correlation was obtained with σ values. These data indicate that a negative charge is developed in the transition state for the isomerization pathway (Schemes 3, 4). In other words, electron-withdrawing groups in the aromatic ring increase the rate of isomerization and also of decarboxylation and hydrolysis.

Scheme 2.



$$\frac{d[T_2]}{dt} = (k_d + k_n[H_2O] + k_1)[T_2] - [T_1]$$

$[T_2]_0 = [T_2] + [T_d] + [T_H] + [T_1]$ (Material balance equation)

$$[T_1]_0 = [T_2]_0 + [T_2] + [T_d] + [T_H]$$

$$-\frac{d[T_2]}{dt} = k[T_2] - k_{-1}([T_2]_0 - [T_2] - [T_d] - [T_H]),$$

$$k = k_d + k_H H_2O + k_1$$

Since $[H_2O] << [T_2]$ or $[T_1]$, any change in $[H_2O]$ is negligible.

$$-\frac{d[T_2]}{dt} = (k + k_{-1})[T_2] - k_{-1}([T_2]_0 - [T_d] - [T_H])$$

When equilibrium establishes: $d[T_2]/dt = 0$

$$(T_2)_0 - [T_d] - [T_H] = \frac{(k + k_{-1})}{k_{-1}} (T_2)_e$$

$$-\frac{d[T_2]}{dt} = (k + k_{-1})[T_2] - (k + k_{-1})[T_2]_e$$

$$-\frac{d[T_2]}{dt} = (k + k_{-1})([T_2] - [T_2]_e)$$

$$\ln\left[\frac{[T_2] - [T_2]_e}{[T_2]_0 - [T_2]_e}\right] = -(k + k_{-1})t,$$

where $(k + k_{-1}) = k_{obs}$ (1)

Two mechanisms of the N^2–N^1-isomerization of tetrazoles can be considered: intermolecular (dissociation–recombination, e.g., an ionic mechanism) and intramolecular (concerted 1,2-shift). Following the first of these, 2-alkoxycarbonyl-5-aroxytetrazoles dissociate completely to form tetrazolide anion and methoxycarbonyl cation (Scheme 3). Scheme 4 shows two types of intramolecular concerted mechanism of the equilibrium N^2–N^1-isomerization.

Table 5. Relative stabilities (kcal/mol) and dipole moments (D) of 1(2)-methoxycarbonyl-5-(*p*-X-C_6H_4O)-tetrazoles, calculated by the AM1 method

X	Relative stability of the 1-isomer with respect to the 2-isomer[a]	Dipole moment	
		1-isomer	2-isomer
CH_3	7.50 (**I**/**II**)	6.30	1.90
H	8.30 (**III**/**IV**)	3.40	1.70
Cl	8.10 (**VII**/**VIII**)	3.40	1.70
NO_2	6.70 (**XIII**/**XIV**)	4.90	5.60

[a] In parentheses are given the corresponding compound numbers.

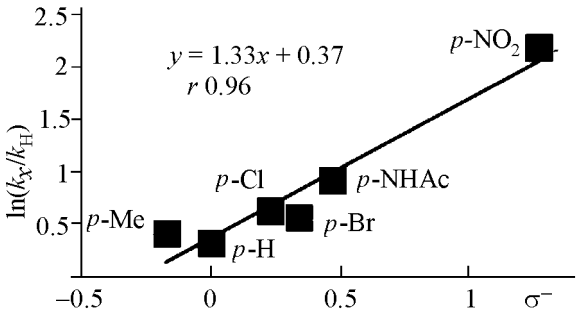
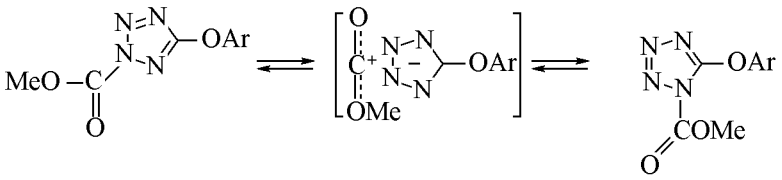


Fig. 4. Hammett correlation for the rate of disappearance of 2-methoxycarbonyl-5-(*p*-XC_6H_4O)tetrazoles in $CDCl_3$–DMSO-d_6 (75 : 25, w/w) at room temperature: $y = 1.3334 \times x + 0.3661$; $r = 0.9648$.

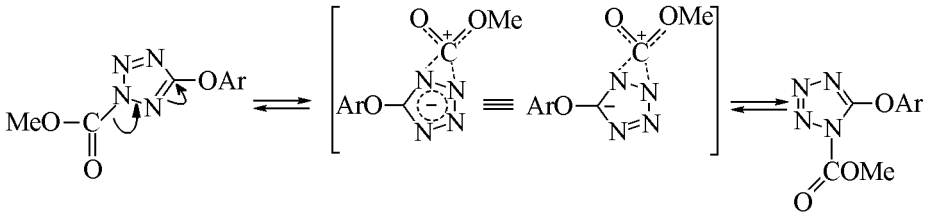
Initially, the concerted mechanisms were considered (Scheme 4). However, the Hammett plot for the isomerization ($\rho^- = 1.33$, $r = 0.965$, for *p*-XC_6H_4O groups at the 5-position of tetrazoles, X = NO_2, AcNH, Br, Cl, H, CH_3) favor an ionic mechanism. Concerted reactions are generally characterized by smaller ρ values. However, a concerted mechanism of type A cannot be ruled out. Mechanism B is excluded because of the positive ρ value.

The rate of isomerization and side reactions (hydrolysis and decarboxylation) increases in going to more polar solvents: C_6D_5N, CD_3OD, CD_3CN, and D_2O. This was the first indication that the reaction follows an ion pair mechanism (Table 3). Concerted mechanisms are less sensitive to the solvent polarity. In weakly polar solvents (such as CCl_4, $CDCl_3$, and CD_3COCD_3) the isomerization is very slow. Neither isomerization no side reactions were observed with tetrazoles having NO_2, AcNH, Br, Cl, H, or CH_3 group in the *para*-position of the 5-phenoxy substituent. The isomerization was not accompanied by side reactions when the substrates had CH_3O, CH_3CH_2O, 2,4,6-trimethylphenoxy, or 2,6-dimethylphenoxy groups in position *5* of the heteroring.

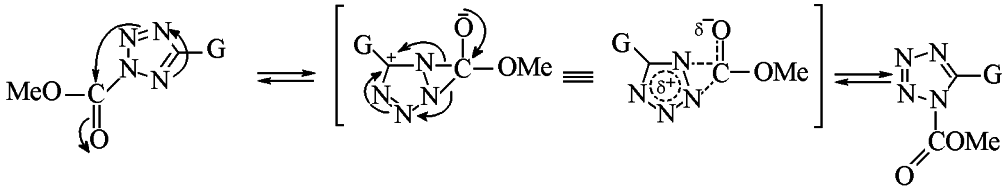
Scheme 3.
Ionic intermolecular isomerization mechanism



Scheme 4.
A: Concerted intramolecular isomerization mechanism with formation of tetrazolide anion

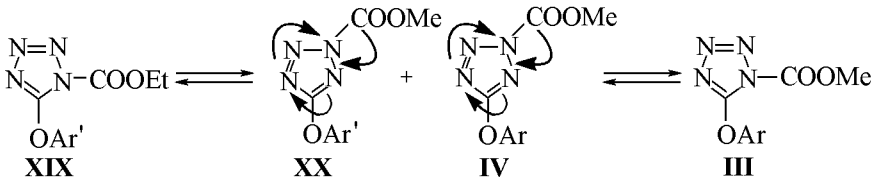


Ar = *p*-XC_6H_4; X = NO_2, AcNH, Br, Cl, H, CH_3.
B: Concerted intramolecular isomerization mechanism with formation of tetrazolium cation

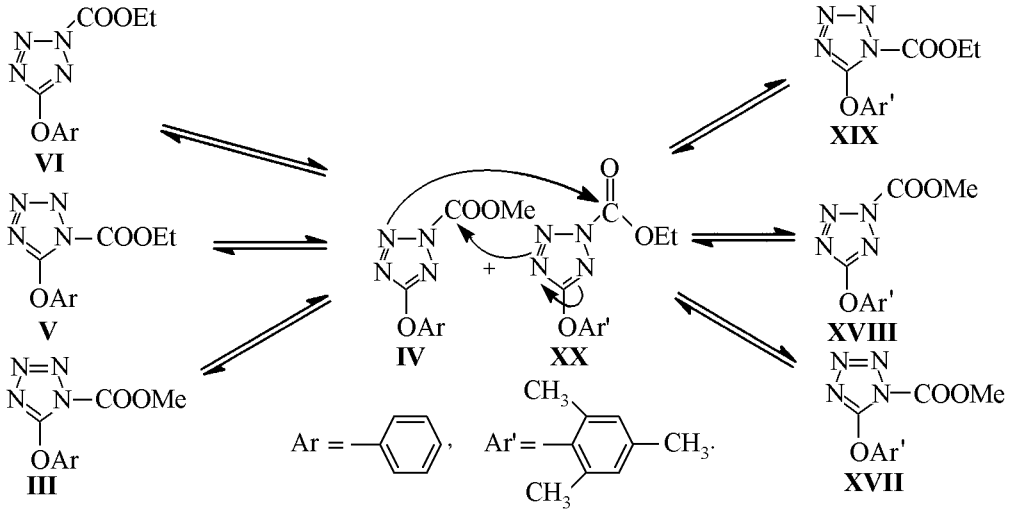


G = CH_3S, CH_3O, CH_3CH_2O.

Scheme 5.
Intramolecular concerted mechanism of equilibrium isomerization



Scheme 6.
Intramolecular ionic mechanism of equilibrium isomerization



Special experiments were carried out in order to verify the proposed mechanisms. A 1 : 1 mixture of 2-ethoxycarbonyl-5-(2,4,6-trimethylphenoxy)tetrazole (**XX**) and 2-methoxycarbonyl-5-phenoxytetrazole (**IV**) was dissolved in $CDCl_3$–DMSO-d_6 (75 : 25, w/w), and the rate of disappearance of both substrates was monitored by ^{1}H NMR spectroscopy. We expected to observe four tetrazoles at the equilibrium for the concerted mechanism (Scheme 5) and eight tetrazoles for the ionic mechanism (Scheme 6). Unfortunately, all the signals corresponding to the CO_2CH_3 group of N^1-tetrazoles appeared at δ 3.80 ± 0.05 ppm. When the mixture of tetrazoles **IV** and **XX** was injected into a mass spectrometer, no molecular ion peaks was observed (due to loss of methoxycarbonyl group). Neither the mixture of **IV** and **XX** nor tetrazole **IV** in solution ($CDCl_3$–DMSO-d_6, 75 : 25) showed the molecular ion peak even at lower ionization energies (10 eV). Pure solid tetrazoles or their solution in chloroform give strong molecular ion peaks; for example, compound **IV** showed the molecular ion peak with *m*/*z* 220 (34%) at 70 eV. The loss of methoxycarbonyl group in solution is a good evidence for at least partial ionization of substituted tetrazoles. This eliminates the possibility of intramolecular concerted mechanism in $CDCl_3$–DMSO-d_6 (75 : 25).

The rate constants for disappearance of each tetrazole in a 1 : 1 mixture of **XX** and **IV** in solution differ from those found for solutions of individual tetrazoles **IV** and **XX** (Table 6). Therefore, addition of tetrazole **IV** affects the rate of disappearance of tetrazole **XX** in solution and vice versa.

Table 6. Rate constants of the isomerization of pure 2-methoxycarbonyl-5-aroxytetrazoles and their 1 : 1 mixtures with 2-ethoxycarbonyl-5-aroxytetrazoles

Compound no.	R	Ar	$k_{ap} \times 10^6$, [a] s^{-1}	$k_{ap} \times 10^3$, [b] s^{-1}
IV	Me	Ph	3.89	–
XVIII	Me	Mes	6.22	2.0
VI	Et	Ph	4.03	5.1
XX	Et	Mes	0.66	5.1

[a] Pure N^2-tetrazoles.

[b] 1 : 1 Mixtures of 2-methoxycarbonyl- and 2-ethoxycarbonyl-5-aroxytetrazoles [Eq. (1)].

The following conclusions can be drawn from the results of our study of the kinetics and mechanism of isomerization of 2-methoxycarbonyl-5-(*p*-X-phenoxy)-tetrazoles. According to the ^{1}H NMR and IR data, in polar solvents the equilibrium is displaced toward the more polar N^1-isomer. In the solid phase N^2-tetrazoles predominate. The isomerization rate increases with rise in solvent polarity and increase in the electron-withdrawing power of the substituent in position *5* of the heteroring. A good correlation is observed between $\ln(k_X/k_H)$ and Hammett constants σ^- (ρ^- = 1.33, r = 0.965). The isomerization follows the intermolecular ion pair mechanism in polar solvents. In less polar solvents, the intramolecular concerted mechanism of type A is favored. In none of the systems under study azide tautomer was detected. In keeping with the calculated (AM1) total energues and dipole moments, N^1-tetrazoles are more stable and more polar than their N^2-isomers. The higher stability of N^1-tetrazoles (except for compound **XIII**) is responsible for displacement of the equilibrium toward the N^1-isomer in polar solvents.

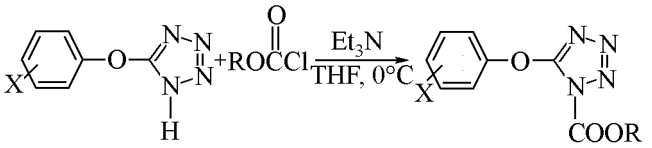
EXPERIMENTAL

The elemental analysis was determined at the Tarbiat Modarres University, Iran. The melting points were determined using a Gallenkamp apparatus and are uncorrected. All starting compounds and solvents were purified by standard procedures prior to use. The ^{1}H NMR spectra were recorded in $CDCl_3$–DMSO-d_6 (75 : 25, by weight). 2-Alkoxycarbonyl-5-(*p*-X-phenoxy)tetrazole, 80 mg, was dissolved in 0.84 g of the mixed solvent. The solution was placed in an NMR ampule, and the isomer ratio was measured at specified time intervals (depending on the substituent on C^5) at room temperature. The AM1 calculations were performed using HyperChem 5.02 software [27].

1*H*-Tetrazoles were synthesized by the procedures reported in [16, 29]. The conditions for synthesis of 2-methoxycarbonyl-5-(*p*-X-phenoxy)tetrazoles are given for X = H, CH_3, NO_2, $NHCOCH_3$, Cl, and Br. All 1*H*-tetrazoles reacted with methyl or ethyl chloroformate in anhydrous THF in the presence of triethylamine. The results are summarized in Table 7.

2-Alkoxycarbonyl-5-(*p*-X-phenoxy)tetrazoles [X = H, CH_3, Cl, Br, $NHCOCH_3$, NO_2, 2,6-$(CH_3O)_2$]. 5-(*p*-X-Phenoxy)tetrazole, 5.91 mmol, and freshly distilled alkyl chloroformate, 6.5 mmol, were dissolved in 30 ml of THF dried over metallic sodium. The solution was cooled to 0°C, and a solution of 0.9 ml (6.5 mmol) of triethylamine in 10 ml of anhydrous THF was added dropwise. The mixture was stirred for 2 h and filtered, and the precipitate was washed with anhydrous THF (3 × 10 ml). The filtrate was evaporated under reduced pressure at 30°C. Dry diethyl ether was added to the viscous residue until the solution became cloudy, and the latter was left overnight in a refriferator. Crystals of 2-alkoxycarbonyl-5-(*p*-X-phenoxy)tetrazole were filtered off and washed with 10 ml of cold diethyl ether. The ^{1}H NMR

Table 7. Synthesis of 1-alkoxycarbonyl-5-aroxytetrazoles by reaction of 5-aroxytetrazoles with methyl and ethyl chloroformates



Comp. no.	X	R	Yield, %	mp (decomposition point), °C
II	*p*-CH_3	Me	52	72–73 (100)
IV	H	Me	55	68–69 (97–98)
VI	H	Et	57	54–56 (98)
VIII	*p*-Cl	Me	80	90–91 (96–97)
X	*p*-Br	Me	94	77–78 (106)
XII	*p*-NHAc	Me	92	109 (110–111)
XIV	*p*-NO_2	Me	72	88 (91)
XVI	2,6-$(MeO)_2$	Me	68	171–173 (125)
XVIII	2,4,6-Me_3	Me	70	104–105 (114)
XX	2,4,6-Et_3	Et	65	93–94 (94–95)

Table 8. Spectral parameters of *N*-methoxycarbonyl-5-(*p*-X-phenoxy)tetrazoles

X	IR spectrum, ν, cm^{-1}		^{1}H NMR spectrum,[a, b] δ, ppm	
	N^2-isomer[c]	N^1-isomer[b]	N^1-isomer	N^2-isomer
CH_3	1810 (**II**)	1750 (**I**)	3.75 (**I**)	4.20 (**II**)
H	1804 (**IV**)	[d]	3.80 (**III**)	4.25 (**IV**)
Cl	1797 (**VIII**)	1750 (**VII**)	3.80 (**VII**)	4.25 (**VIII**)
Br	1797 (**X**)	1750 (**IX**)	3.85 (**IX**)	4.30 (**X**)
NHAc	1690[g], 1750 (**XII**)	1690[e], 1797 (**XI**)	3.80 (**XI**)	4.30 (**XII**)
NO_2	1797 (**XIV**)	1750 (**XIII**)	3.75 (**XIII**)	4.30 (**XIV**)

[a] Chemical shifts of CO_2CH_3; in parentheses are given compound numbers.
[b] In $CDCl_3$–DMSO-d_6 (75 : 25, w/w) at the equilibrium state.
[c] In KBr.
[d] Not detected.
[e] Amide carbonyl frequency.

Table 9. Elemental analyses of 2-alkoxycarbonyl-5-(*p*-X-phenoxy)tetrazoles[a]

Compound no.	Found, %			Formula	Calculated, %		
	C	H	N		C	H	N
II	51.28	4.30	23.92	$C_{10}H_{10}N_4O_3$	51.80	4.34	24.49
IV	49.09	3.66	25.45	$C_9H_8N_4O_3$	49.25	3.62	25.54
VI	51.28	4.30	23.92	$C_{10}H_{10}N_4O_3$	51.62	4.27	24.04
VIII	42.45	2.77	22.00	$C_9H_7ClN_4O_3$	42.44	2.75	22.34
X	36.14	2.36	18.73	$C_9H_7BrN_4O_3$	36.10	2.32	19.38
XX	55.51	5.84	20.28	$C_{12}H_{14}N_4O_3$	56.17	5.78	20.27

[a] Compounds **I**, **III**, **V**, **VII**, **IX**, and **XI**–**XIX** were reported in [29].

Table 10. FT-IR and ^{1}H NMR spectra of 2-alkoxycarbonyl-5-(*p*-X-phenoxy)tetrazoles

Compd. no.	FT-IR spectrum (KBr), ν, cm^{-1}	^{1}H NMR spectrum, δ, ppm (J, Hz)
II	3046 m, 2966 m, 2950 m, 1810 s, 1549 s, 1360 s, 1193 s, 1078 m, 978 m, 830 s, 749 s	(DMSO, $CDCl_3$): 2.40 s (3H), 4.25 s (3H), 7.20–7.50 m (4H)
IV	3181 m, 2910 m, 2890 w, 1804 s, 1549 s, 1193 s, 682 m	(DMSO, $CDCl_3$): 4.25 s (3H), 7.20–7.70 m (5H)
VI	3095 w, 2993 m, 2955 w, 1797 s, 1543 s, 1382 s, 1173 s, 965 s	(DMSO, $CDCl_3$): 1.50 t (3H, 8), 4.70 q (2H, 8), 7.20–7.70 m (5H)
VIII	3113 m, 3100 w, 2959 w, 2955 w, 1797 s, 1549 s, 1488 m, 1367 s, 1233 s, 1078 s, 978 s, 837 m, 750 m	(DMSO, $CDCl_3$): 4.25 s (3H), 7.30–7.70 m (4H)
X	3107 m, 2966 m, 1797 s, 1549 s, 1481 m, 1367 m, 1193 s, 1072 s, 830 s, 749 s	(DMSO, $CDCl_3$): 4.30 s (3H), 7.25–7.90 m (4H)
XII	3369 m, 3200 w, 3170 w, 3073 w, 1797 s, 1690 s, 1616 m, 1549 s, 1508 s, 1441 s, 1193 s, 978 m, 837 s	(DMSO, $CDCl_3$): 2.10 s (3H), 4.20 s (3H), 7.20–7.50 m (2H), 10.05 s (1H)
XIV	3120 m, 1087 m, 1797 s, 1535 s, 1448 s, 1360 s, 1226 s, 870 s, 749 s	(DMSO, $CDCl_3$): 4.30 s (3H), 8.50 d (2H, 9), 7.80 d,(2H, 9)
XVI	3100 w, 3000 m, 2920 m, 2830 m, 1805 s, 1610 s, 1535 s, 1480 s, 1440 s, 1365 s, 1310 s, 1230 s, 1110 s, 975 s, 820 s, 760 s	(DMSO, $CDCl_3$): 2.15 s (6H), 4.30 s (3H), 7.30 d (2H, 9), 7.70 d (2H, 9)
XVIII	3045 w, 2995 w, 2919 w, 1797 s, 1549 s, 1367 m, 1193 m, 984 m, 749 m	(DMSO, $CDCl_3$): 2.15 s (6H), 2.30 s (3H), 4.25 s (3H), 7.10 s (2H)
XX	3005 m, 2925 m, 1797 s, 1549 s, 1481 m, 1193 s, 857 m, 756 m	($CDCl_3$): 1.50 t (3H, 8), 2.15 s (6H), 2.30 s (3H), 4.70 q (2H, 8), 7.05 s (2H)

and FT-IR spectra of the products are given in Tables 8 and 10, and their elemental analyses are collected in Table 9. The structure of the tetrazoles listed in Table 7 was established by converting them into the corresponding *N*-methyltetrazoles [27].

Typical procedure for measurement of the rate of disappearance of 2-alkoxycarbonyl-5-aroxytetrazoles. A high-precision ^{1}H NMR ampule was charged with 80 mmol of 2-methoxycarbonyl-5-aroxytetrazole, 0.84 g of $CDCl_3$–DMSO-d_6 (75 : 25), and tetramethylsilane as internal reference. The progress of the reaction was monitored by measuring ^{1}H NMR spectra at room temperature (Fig. 1). The chemical shifts of the CH_3OCO protons of each isomer were preliminarily found from the ^{1}H NMR spectra of pure 1- and 2-substituted tetrazoles [16, 27]. The relative concentrations of the reactants and the products were calculated from the corresponding signal intensities (Figs. 2, 3). The intensities of the CH_3OCO signal of the reagent and of the CH_3OCO or CH_3N signal of the products were normalized with respect to the aromatic proton signal whose intensity remained unchanged during the process. The rate constants were calculated by

Eq. (1), and the molal concentration [*X*], Mn, by Eq. (2):

$$[X] = 4/3(S_{Me}/S_{arom})\frac{m_T}{m_{solv}\,M_T}, \quad (2)$$

where m_T, m_{solv}, and M_T are, respectively, the weight of tetrazole (80 mmol), solvent (0.84 g), and molecular weight of tetrazole; S_{Me} and S_{arom} are the areas under the signals from methyl and aromatic protons; the coefficient 3/4 should be replaced by 5/3 in the case of 5-phenoxytetrazole and by 2/3 in the case of 5-mesityloxytetrazole.

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