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2-Alkyl-5-aryltetrazoles as Hydrogen Bond Acceptors

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Abstract—The dissociation constants of the H-complexes formed by 2-alkyl-5-aryltetrazoles and *p*-fluorophenol in carbon tetrachloride (pK_{HB} 0.9–1.3) were determined by Fourier-transform IR spectroscopy. 2-Alkyl-5-aryltetrazoles were found to act as medium-strength hydrogen bond acceptors comparable with diazines. The thermodynamic parameters of the equilibrium formation of H-complex with 2-isopropyl-5-phenyltetrazole were determined. The electronic nature of substituents in the tetrazole ring only slightly affects the pK_{HB} values of tetrazoles.

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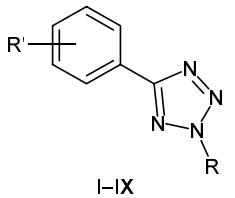
Incomplete protolytic H-bonding equilibria play an important role in most chemical and biochemical processes and are responsible for some physical properties of substances, e.g., their solubility, melting points, the ability to undergo sublimation, kind of crystal lattice, etc. [1, 2]. Formation of H-complexes is typical of nitrogen-containing heterocycles (azoles and azines) which can act as both donor and acceptor of a proton. To some extent, these processes determine their biological activity [3].

As shown previously, compounds containing a tetrazole ring are capable of forming H-complexes with various acids and bases both in solution and in crystal. Hydrogen bond formation with tetrazoles was detected by NMR spectroscopy on different nuclei in solution and in the solid phase [4–6]. IR spectroscopy was used in quantitative studies on H-complex formation between tetrazole ring as proton donor and bases in weakly polar solvents [7–9]. For example, the IR data showed that tetrazole and 1,8-bis(dimethylamino)-naphthalene give 1:1 complexes with a bifurcated hydrogen bond in aprotic solvents and in the solid phase [6, 10, 11]. Kakas et al. [12] examined the electronic absorption, excitation, and fluorescence spectra of 5-(2-cyanophenyl)tetrazole and revealed formation of intramolecular hydrogen bond between the tetrazole ring and cyano group. According to the X-ray diffraction data, tetrazoles in crystal are linked through both intra- and intermolecular hydrogen bonds. Unsubstituted tetrazole molecules are packed to give planar polymer-like layers [13]. Naumenko et al. [14, 15] showed by IR spectroscopy that phenol with N-substituted tetrazoles forms H-complexes in weakly polar solvents. The shift of the stretching vibration frequency of the O–H bond in phenol as a result of hydrogen bonding may be used to predict some physicochemical parameters of N-substituted tetrazoles. Despite a fairly large number of publications concerning hydrogen bonding with tetrazoles, there are no quantitative data on the hydrogen bonding basicity of these compounds.

In the present work we used Fourier-transform IR spectroscopy to determine the hydrogen bonding basicity constants (pK_{HB}) of 2-alkyl-5-aryltetrazoles **I**–**IX** in carbon tetrachloride relative to the standard proton donor, *p*-fluorophenol. The set of the examined compounds includes those having alkyl groups of different sizes at the nitrogen atom and substituents with different electronic natures in positions *3* and *4* of the benzene ring on C^5. Compounds **I**–**IX** are soluble in carbon tetrachloride at a required concentration of 0.005–0.05 M. Thus the set of compounds **I**–**IX** ensured estimation of the effects of both electronic properties of substituents in the 5-phenyl ring and steric factors, which could affect the ability of the tetrazole



I–**IX**

I, R = Me, R' = H; **II**, R = Me, R' = 4-Me; **III**, R = Me, R' = 4-MeO; **IV**, R = Me, R' = 4-Br; **V**, R = *t*-Bu, R' = H; **VI**, R = *i*-Pr, R' = H; **VII**, R = *i*-Pr, R' = 4-Me; **VIII**, R = *i*-Pr, R' = 3-O_2N; **IX**, R = $PhCH_2$, R' = H.

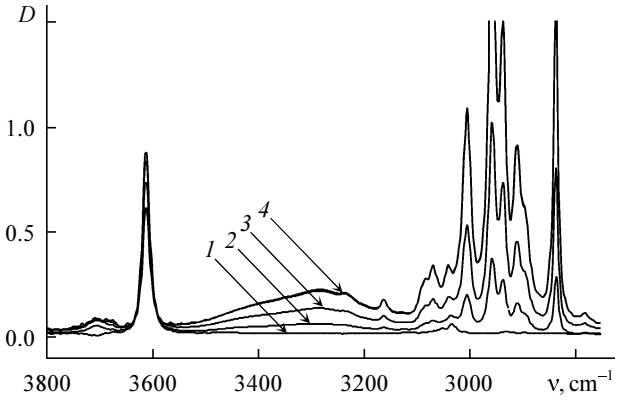
ring to act as proton acceptor in H-complex formation. It should be emphasized that carbon tetrachloride (which exhibits neither acidic nor basic properties) and *p*-fluorophenol are standard solvent and proton donor, respectively, in the determination of hydrogen bonding basicity constants of various organic compounds. Moreover, *p*-fluorophenol is fairly readily soluble in many nonpolar solvents, it gives sharp peaks due to stretching vibrations of the unassociated O–H bond in the IR spectra, is thermally and chemically stable, and it gives no self-associates up to a concentration of 4×10^{-3} M [16]. Therefore, it is possible to compare pK_{HB} values obtained by different authors. Experiments were performed under the conditions excluding possible dimerization of the components in equilibrium mixtures, as well as their interaction with foreign acids and bases.

The dissociation constants of H-complexes [K_f; equilibrium (1)] were calculated on the basis of the classical concepts using Eq. (2). The hydrogen bonding basicity constants (pK_{HB}) were assumed to be equal to the logarithm of K_f to the base 10 ($pK_{HB} \equiv \log K_f$) [16, 17]. The equilibrium concentrations were calculated from the intensity of the stretching vibration band of the unassociated OH group in *p*-fluorophenol.

$$AH + B \underset{}{\overset{K_f}{\rightleftharpoons}} AH\cdots B \qquad (1)$$

$$K_f = \frac{[AH\cdots B]}{[AH]\,[B]} = \frac{AH_0 - [AH]}{[AH](B_0 - AH_0 + [AH])}. \qquad (2)$$

Here, [AH···B] is the equilibrium concentration of H-complex; AH_0 and B_0 are the initial concentrations of the proton donor and base, respectively; and [AH] and [B] are the equilibrium concentrations of the free proton donor and free base, respectively.



IR spectra of solutions of *p*-fluorophenol ($AH_0 = 3.93\times10^{-3}$ M) in carbon tetrachloride in the presence of 2-*tert*-butyl-5-phenyltetrazole (**V**) at a concentration ($B_0\times10^{-2}$, M) of (*1*) 0, (*2*) 0.68, (*3*) 1.34, and (*4*) 2.34.

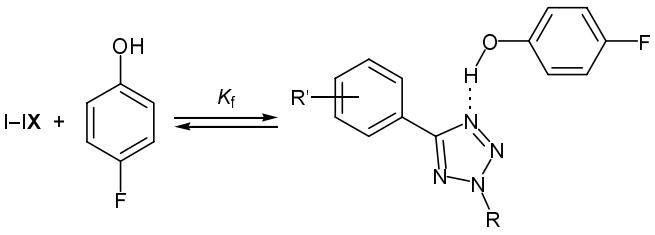
Taking into account that pK_{HB} values depend on the conditions of their determination, the obtained data were checked independently using model hydrogen bond acceptors with known pK_{HB} values. The constants determined in the present work coincided with those available from the literature within experimental error. For example, pK_{HB} of unsubstituted pyridine was estimated at 1.88±0.01 (cf. pK_{HB} = 1.86, 1.88 [17, 18]).

The IR spectra of mixtures of bases **I**–**IX** with *p*-fluorophenol in CCl_4 contained a strong absorption band at 3612–3614 cm^{-1}, corresponding to stretching vibrations of unassociated OH group in *p*-fluorophenol. The signal from associated OH group appeared as a diffuse band with an ill-defined maximum in the frequency range from 3150 to 3500 cm^{-1} (see figure). As the concentration of tetrazoles **I**–**IX** rose, the intensity of the unassociated OH band decreased while the intensity of the band from H-bonded OH group increased. The position of the diffuse band changed insignificantly in the series of tetrazoles **I**–**IX**.

Scheme 1 illustrates the formation of 1 : 1 H-complexes by tetrazoles **I**–**IX** with *p*-fluorophenol. It should be noted that 2-substituted tetrazole ring possesses three pyridine-type nitrogen atoms capable of acting as basic centers. According to theoretical and experimental data, the preferential basic center in both 1- and 2-substituted tetrazoles is nitrogen atom in position *4* of the heteroring. The largest negative charge is localized just on that nitrogen atom, and proton addition to N^4 gives the most thermodynamically favorable tetrazolium ion [19, 20]. However, special studies are necessary to unambiguously determine which nitrogen atom of the tetrazole ring is involved in hydrogen bonding.

The pK_{HB} values of compounds **I**–**IX** calculated by Eq. (2) at different tetrazole concentrations coincide within experimental error (±0.01–0.03 log unit). As follows from the data given in table, 2-substituted tetrazoles are fairly strong hydrogen bond acceptors.

Scheme 1.



The difference in pK_{HB} values of tetrazoles, on the one hand, and strongly basic azines and azoles, on the other, is not as significant as the difference in the corresponding pK_{BH^+} values. For example, the pK_{BH^+} values of pyridine, pyrazine, and 2-methyl-5-phenyltetrazole (**I**) are 5.23 [21], 0.51 [21], and –3.27 [22], respectively, while the corresponding pK_{HB} values are 1.86 [17], 1.22 [17], and 1.16. Presumably, the reason is the following: the crucial factor in the complete proton transfer is thermodynamic stability of the conjugate acid, while in the formation of H-complex the charge on the basic center and its spatial accessibility may be of principal importance. The presence of vicinal heteroatoms in the tetrazole ring could give rise to H-complexes with bifurcated hydrogen bond.

The data in table indicate that electronic nature of the substituents in the tetrazole ring insignificantly affects pK_{HB}, though acceptor groups slightly reduce pK_{HB} value. No appreciable steric effect is observed upon replacement of 2-methyl group by *tert*-butyl, which is consistent with the above assumption that the basic center in the formation of H-complexes is the nitrogen atom in position *4* of the heteroring.

The equilibrium constants K_f for 2-isopropyl-5-phenyltetrazole (**VI**) were measured at different temperatures in the range from 20 to 36°C. The temperature dependence of K_f in the given interval is weak (see table); it is described by linear relation (3).

$$\log K_f = (650\pm40)/T - (1.0\pm0.2); \quad (3)$$
$$n = 5,\ r = 0.99,\ s = 0.005.$$

Using Eq. (3) we calculated thermodynamic parameters of the complex formation equilibrium for tetrazole **VI**: $\Delta H_{298} = -12.4\pm0.7$ kJ/mol, $\Delta S_{298} = -20\pm2$ J × mol^{-1} K^{-1}. These parameters correspond to formation of a medium-strength hydrogen bond between tetrazole ring and standard proton donor [1].

EXPERIMENTAL

The IR spectra of solutions containing mixtures of *p*-fluorophenol with tetrazoles **I**–**IX** were recorded in the frequency range from 4000 to 2500 cm^{-1} on a Shimadzu FTIR-8400 spectrometer using 1-cm glass hermetically capped cells placed in a temperature-controlled unit. The temperature was maintained with an accuracy of ±0.1°C. Commercial *p*-fluorophenol (from Aldrich) containing more than 99% of the main substance was additionally purified and dehydrated by vacuum sublimation and was stored over P_2O_5. Carbon tetrachloride was additionally purified and dehydrated by triple distillation over P_2O_5 and was stored over 4-Å molecular sieves. The absence of moisture in the solvent was checked by IR spectroscopy at a frequency corresponding to O–H stretching vibrations of water molecule. 2,5-Disubstituted tetrazoles **I**–**IX** were synthesized and purified by known procedures [23, 24] and were stored over P_2O_5 under reduced pressure; their physical and spectral properties were consistent with published data. In keeping with the recommendations given in [17], the concentration of *p*-fluorophenol in working solutions did not exceed 4×10^{-3} M; the concentration of bases **I**–**IX** was selected in such a way that the fraction of associated *p*-fluorophenol be 20 to 80% of the overall amount of the donor. Table contains pK_{HB} values averaged from 3–4 measurements at different base concentrations.

Hydrogen bonding basicity constants pK_{HB} of 2-alkyltetrazoles **I**–**IX** with respect to *p*-fluorophenol in CCl_4 at 25°C

Compound no.	R	R'	pK_{HB}
I	Me	H	1.16±0.02
II	Me	4-Me	1.14±0.03
III	Me	4-MeO	1.28±0.03
IV	Me	4-Br	0.98±0.02
V	*t*-Bu	H	1.41±0.02
VI	*i*-Pr	H	1.16±0.02[a]
VII	*i*-Pr	4-Me	1.22±0.01
VIII	*i*-Pr	3-O_2N	0.96±0.01
IX	$PhCH_2$	H	1.15±0.02

[a] pK_{HB} (temperature, °C): 1.19 (20), 1.12 (29), 1.10 (32), 1.08 (36).

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