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BASE-INDUCED C-H/C-D EXCHANGE IN TETRAZOLES AND TETRAZOLIUM CATIONS

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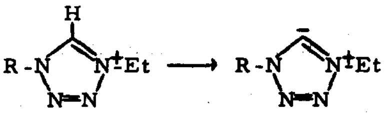
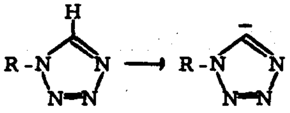
The kinetic acidity of a C-H bond which is sp^2 hybridized at carbon can be dramatically enhanced by the introduction of adjacent positive charges and electron withdrawing substituents.[1, 2] Among readily accessible substrates the compounds expected to yield the most highly stabilized carbanions (which are not π-delocalized in a classical sense) are the 1,4-disubstituted tetrazolium cations (I).[3] Similarly, 1-substituted tetrazoles (III) should be among the strongest formally neutral C-H acids of this type.



I II



III IV

A: R = p-Anisyl
B: R = p-Tolyl
C: R = Phenyl
D: R = p-Chlorophenyl
E: R = p-Nitrophenyl
F: R = Ethyl

In this communication we confirm these predictions and demonstrate the effect of substituent on the acidity of the tetrazole ring.

The rates of deuterium incorporation at C_5 of a series of 1-aryl-4-ethyltetrazolium cations (I)[4] in DCl-D_2O and CF_3CO_2D-D_2O solutions are listed in Table I and are in accord with expectation. The p-nitrophenyltetrazolium salt (IE) is in fact so acidic that its deprotonation is almost too fast to measure in 9.0 N CF_3CO_2D. That these H/D exchanges are in

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Table I

H/D Exchange Kinetics for 1,4-Disubstituted Tetrazolium Salts (I) at 30°C[a]

Cpd	R =	NMR (τ)[b]	$t_{\frac{1}{2}}$ in 3.83 N DCl-D_2O[c]	$t_{\frac{1}{2}}$ in 6.50 N DCl-D_2O	$t_{\frac{1}{2}}$ in CF_3CO_2D-D_2O Solutions[d] (min)			
					6.56 N	7.94 N	9.01 N	10.75 N
IA	p-Anisyl	-1.36	2.9 min	--	--	--	21.8	--
IB	p-Tolyl	-1.39	2.4	23 min	2.5	6.2	17.7	--
IC	Phenyl	-1.46	1.8	e	--	--	12.2	--
ID	p-ClPhenyl	-1.53	1.2	9.4[f]	--	--	4.8	223
IE	p-NO_2Phenyl	-1.70	--	2.2	--	--	(0.9)	23[g]
IF	Ethyl	-0.45[h]	--	--	20	55	203	--

Table II

H/D Exchange Kinetics for 1-Substituted Tetrazoles (III) at 30°C[a]

Cpd	R =	NMR (τ)[i]	$t_{\frac{1}{2}}$ in solvent 1[j]	$t_{\frac{1}{2}}$ with Et_3N in MeOD		$t_{\frac{1}{2}}$ at pD = 10.1[k]
				0.47 M Et_3N	0.27 M Et_3N	
IIIA	p-Anisyl	+0.16	57.3 min	--	--	--
IIIB	p-Tolyl	+0.10	47.3	7.3 min	--	--
IIIC	Phenyl	+0.02	22.8	4.2	6.8 min	--
IIID	p-ClPhenyl	-0.01	12.8	--	--	--
IIIE	p-NO_2Phenyl	-0.19	1.5	--	--	--
IIIF	Ethyl	+0.60	--	65	--	21.5 min[l] 6.0 min[l] 1.8 min[l]

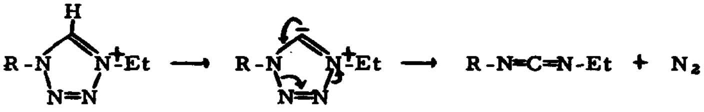
[a] Rates measured by NMR (Varian A60A) using the probe as a thermostat; the reproducibility is about 10%; under a given set of conditions exchange is nicely first order over two half lives; substrate concentration is approximately one molar; little rate variation between 0.5-1.5 M. [b] Of C_5-H; in 3.83 N DCl-D_2O; measured against external TMS. [c] Using the tetrazolium chloride as substrate. [d] Using the tetrazolium fluoroborate as substrate. [e] $t_{\frac{1}{2}}$ = 3.4 min in 4.43 N DCl-D_2O and 67 min in 7.60 N DCl-D_2O. [f] Also 3.9 min in 5.4 N DCl-D_2O. [g] Also 430 min in 11.97 N CF_3CO_2D-D_2O. [h] In 4.50 N CF_3CO_2D in D_2O; $t_{\frac{1}{2}}$ in this system = 5.8 min. [i] Of C_5-H in solvent system 1. [j] Solvent 1 is 0.157 M piperidine in 9.39 M DMF and 6.34 M MeOD; $t_{\frac{1}{2}}$ is average of 2 runs; [k] Measured value uncorrected for difference between pH and pD; solution made from 0.1 M $NaHCO_3$ in D_2O. [l] Rates at 30°, 40°, and 50°C respectively.

fact base-induced is readily seen from an examination of the effect of acid concentration on reaction rate. It is more difficult to identify the base but it is probably some combination of water and the conjugate base of the acid (Cl^- or $CF_3CO_2^-$).[5] When the 1,4-diethyltetrazolium cation (IF) is exchanged in pure CF_3CO_2D at 78°C the deuterium incorporation rate varies with the nucleophilicity of the substrate anion in accord with this hypothesis: fluoroborate salt: $t_{\frac{1}{2}}$ = 5100 min., p-toluenesulfonate salt: $t_{\frac{1}{2}}$ = 690 min., chloride salt: $t_{\frac{1}{2}}$ = 225 min. The non-nucleophilic 1-p-nitrophenyl-4-ethyltetrazolium fluoroborate undergoes base catalyzed deprotonation with a $t_{\frac{1}{2}}$ = 160 min. in pure CF_3CO_2D at 78°C. The Hammett ρ for H/D exchange is +0.76 in 3.83 N $DCl-D_2O$ and +1.4 in the less polar 9.0 N $CF_3CO_2D-D_2O$ where electronic effects are more easily transmitted. We interpret this to indicate that there is very little contribution of the carbene structure (V) to the stabilization of the ylid component (II) of the transition state of the deprotonation process. If (V) were important we would also expect stabilizing contributions from the zwitterion structure (VI) and because of this a much more positive ρ.

V VI

From the data in Table II it is readily apparent that the neutral tetrazoles (III) are easily deprotonated by amine bases. The Hammet ρ in this system is +1.3 in piperidine-MeOD-DMF. The deprotonation of 1-ethyltetrazole has a high activation energy, 24.1 Kcal/mole[6] and a positive activation entropy $\Delta S^{\ddagger}$ = +22 cal/mole deg.

The tetrazolium salts (I) all undergo ring scission to the carbodiimides (VII) in a much slower reaction demonstrating the presence of the ylid (II) as a real intermediate.



I II VII

As anticipated these cleavage rates increase with increasing base concentration and with the substrate; p-anisyltetrazolium cation has a $t_{\frac{1}{2}}$ of ca 3 min at pH 6.5 while at the other extreme p-nitrophenyltetrazolium cation has a $t_{\frac{1}{2}}$ of ca 1 min at pH 4.6 at 25°, a rate difference of about 10^2. The kinetics were run by following the disappearance of I in the ultraviolet and by volumetric measurement of nitrogen evolution. The carbodiimides were always either isolated or trapped with water (H^+ or OH^- catalysis), hydrogen sulfide or picric acid. The synthetic consequences of this ring opening will be considered in another paper.[7]

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REFERENCES

[1] For discussion see: R.A. Olofson, W R. Thompson, and J.S. Michelman, J. Am. Chem. Soc., 86, 1865 (1964).

[2] R.A. Olofson and J.M. Landesberg, ibid., 88, 4263 (1966); R.A. Olofson, J. M. Landesberg, K.N. Houk, and J.S. Michelman, ibid., 88, 4265 (1966).

[3] 5-Unsubstituted-4-aryl-1,2,3,4-oxatriazolium or thiatriazolium cations should be more acidic but these are unknown and not obviously accessible. Some of these tetrazolium cations are even more acidic than the dications of T J. Curphey (ibid., 87, 2063 (1965)).

[4] The tetrazolium salts are all easily prepared by alkylation of the known 1-aryltetrazoles (R.G. Fallon and R.M. Herbst, J. Org. Chem., 22, 933 (1957)) with triethyloxonium fluoroborate. Chloride salts were obtained by passing the appropriate fluoroborate salts through IRA 401 anion exchange resin in the chloride form using a 0.02 N HCl eluent. All these new compounds gave satisfactory elemental analyses.

[5] It is impossible for OD^- to be the active base; the rate constant would then require that the reaction be faster than diffusion control; the rate also decreases much faster with increasing acid concentration than expected from such a situation.

[6] $\Delta H^{\ddagger}$ for the exchange of 1,4-diethyltetrazolium cation (IF) in 9.0 N CF_3CO_2D-D_2O between 30 and 60°C is slightly larger: 25.6 Kcal.

[7] R.A. Olofson, D.M Zimmerman, and A.C. Rochat, unpublished results.