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MECHANISM OF THE NEUTRAL HYDROLYSIS OF 1-ACYL-1,2,4-TRIAZOLES
A PROTON INVENTORY STUDY

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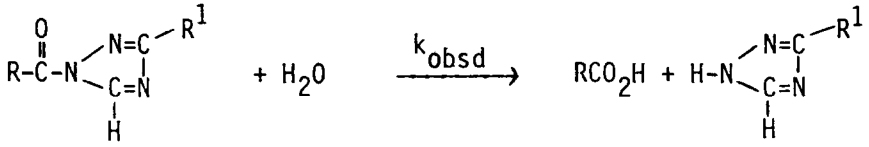
The pH-independent hydrolysis of acyl-activated carboxylic esters is of current interest since it constitutes a useful probe for the effect of hydrophobic hydration on hydrolysis reactions in highly aqueous media.[1] Recently we have found that the "water" reaction of 1-acyl-1,2,4-triazoles also responds to varying water ordering effects.[2] The purpose of the present study has been to delineate a likely mechanism for the neutral hydrolysis of these activated carboxamides.

Pseudo-first order rate constants (k_{obsd}; independent of pH in at least the region pH 3-5), activation parameters, solvent deuterium isotope effects, and Brönsted β coefficients for the neutral hydrolysis of the triazole derivatives 1-12 are listed in Table I. The magnitudes of k_{H_2O}/k_{D_2O} as well as the large negative entropies of activation are clearly in the range expected for water-catalyzed hydrolysis reactions[3] and are reconcilable with a mechanism involving water-catalyzed nucleophilic attack of water at the amide carbonyl moiety. In this mechanism a second water molecule is acting as a general base in the carbonyl addition step. Expulsion of the triazolyl anion from a tetrahedral intermediate then leads to products,[4] as has also been proposed[5] for the "water" reaction of methoxyamine with 1.



1-12; R en R^1: see Table I

Since several types of activated complexes, differing in the amount of charge separation and covalent bonding, can be imagined,[6] the triazoles 1, 4 and 9 were submitted to proton inventory experiments in order to determine the number of protons contributing to the solvent deuterium isotope effect. Thus, the rate constants in H_2O-D_2O mixtures (k^n_{obsd}; n = deuterium atom fraction) are related to the rate constant in H_2O (k^h_{obsd}) by equation (1),[7] in which TS and GS refer to transition state and ground state, respectively, and ϕ^*_i and ϕ_j are the isotopic

$$k^n_{obsd} = k^h_{obsd} \prod_i^{TS} (1-n+n\phi^*_i) \Big/ \prod_j^{GS} (1-n+n\phi_j) \qquad (1)$$

Table I. Pseudo-First Order Rate Constants, Activation Parameters, Solvent Deuterium Isotope Effects and Brönsted Coefficients for the Neutral Hydrolysis[a] of 1-Acyl-1,2,4-Triazoles **1**-**12** at 25.00 ± 0.05°C.

	R	R^1	$k_{obsd}\cdot 10^4$ (s^{-1},25°C)	k_{H_2O}/k_{D_2O}	ΔH‡ (kcal.mol^{-1})		ΔS‡ (e.u.)		β[b]
					H_2O	D_2O	H_2O	D_2O	
1	CH_3	H	20.9[c]	3.04	10.3	11.3	-36	-35	0.36[d]
2	C_2H_5	H	29.7	3.16	9.9	8.9	-37	-42	
3	n-C_3H_7	H	17.4	3.31	9.1	8.8	-41	-44	
4	i-C_3H_7	H	33.4	3.38	8.4	8.0	-42	-45	0.36
5	p-$CH_3OC_6H_4$	H	3.89	2.66	12.6		-32		
6	p-$CH_3C_6H_4$	H	9.50	2.71					
7	C_6H_5	H	20.9	2.65	11.3	11.0	-33	-36	
8	p-CNC_6H_4	H	207	2.46					
9	p-$NO_2C_6H_4$	H	289	2.40	10.6		-30		0.34
10	CH_2Cl	H	ca. 5900	ca.2.5		8.7		-32	
11	CH_3	C_6H_5	15.4	3.55	9.9	10.6	-38	-39	
12	CH_3	Cl	69.2	2.92	9.5	9.8	-36	-38	

[a] Rate constants (pH 3-5, HCl) were monitored at the wavelength of maximum absorption (λ_m,221-295 nm, CH_3CN) using a Zeiss PMQ II or Beckman model 24 spectrophotometer. Estimated accuracy of k_{obsd}: ± 1.5%; of ΔH‡: ± 0.3 kcal.mol^{-1}; of ΔS‡: ± 1 e.u. [b] Brönsted β-values. [c] Lit.: 17.2.10^{-4}s^{-1} (ref. 5) and 18.3.10^{-4}s^{-1} (ref. 12). [d] Ref. 5.

fractionation factors of all exchangeable transition state protons i and ground state protons j. The analysis is facilitated by the fact that **1**, **4**, and **9** do not possess exchangeable protons. Results are presented in Table II.

In contrast to the neutral hydrolysis of bis(4-nitrophenyl)-carbonate[8] in H_2O-D_2O, there exists no linear relationship between k^n_{obsd} and n. This provides strong evidence that more than one proton undergoes transfer in the transition state for hydrolysis. Excellent agreement between observed and calculated k^n_{obsd} values is obtained for **1** and **9** by means of equation (2) in which $\phi^*_B = (0.69)^\beta$ and ϕ^*_A is calculated from k_{H_2O}/k_{D_2O} and ϕ^*_B.[9] The agreement is somewhat less satisfying for **4** (Table II).

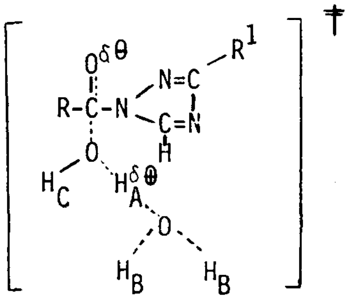
$$k^n_{obsd} = k^h_{obsd}\,(1-n+n\phi^*_A)\,(1-n+n\phi^*_B)^2 \qquad (2)$$

Table II. Pseudo-First Order Rate Constants[a] for the Neutral Hydrolysis of the Triazoles **1**, **4** and **9** in H_2O-D_2O at Different Atom Fractions of Deuterium (n) at 25.00 ± 0.05°C.

1			**4**			**9**		
n	$k^n_{obsd} \cdot 10^4$ (s^{-1})	$k^n_{calc} \cdot 10^4$ (s^{-1})	n	$k^n_{obsd} \cdot 10^4$ (s^{-1})	$k^n_{calc} \cdot 10^4$ (s^{-1})	n	$k^n_{obsd} \cdot 10^4$ (s^{-1})	$k^n_{calc} \cdot 10^4$ (s^{-1})
0.00	20.9		0.00	33.4		0.00	289	
0.35	15.4	15.2	0.20	27.0	27.8	0.25	239	240
0.50	13.3	13.1	0.40	20.7	22.7	0.50	194	195
0.70	10.0	10.4	0.60	15.7	18.0	0.51	193	194
1.00	6.88		0.70	14.2	15.8	0.75	154	155
			0.80	12.4	13.7	1.00	120	
			1.00	9.87				

[a]Calculated values by means of equation (2).

The necessary Brönsted β-values were provided by standard treatment of k_{obsd} values in a series of $RCO_2H/RCO_2^{\ominus}$ (R = CH_3, H, CH_2Cl) buffer solutions. We conclude that three protons (H_A and two H_B protons) contribute to the solvent deuterium isotope effect.[10] Therefore, a likely transition state model may be depicted as



Substituent effects in the series **5**-**9** support the proposed mechanism and reflect the development of negative charge on the carbonyl group in the transition state. Reaction rates can be successfully correlated by the Yukawa-Tsuno equation[11] (3) with r = 0.42 and ρ = 1.48.

$$\log k^X_{obsd}/k^H_{obsd} = \rho\left[\sigma^+ - r(\sigma^+ - \sigma)\right] \tag{3}$$

Finally, we note that the proposed mechanism is essentially different from that originally advan by Staab[12] and later adopted by Potts,[13] involving rate determining acylium ion formation.

References and Notes

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