NH-Acidities of Some Sterically Hindered Ureas†

J. Chem. Research (S), 1997, 220–221†

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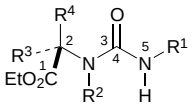
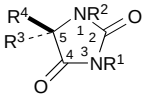
Introduction of an *N*-methyl group in to ethyl *N*-methylhydantoate causes a fourfold decrease in the rate of base-catalysed exchange of the N-H proton; a second methyl group restores the rate to close to that of the *N*-unsubstituted hydantoate; the latter effect is observed for *N*-phenylhydantoates.

Proton exchange in amides and ureas is of continuing interest to biochemistry.[1] The introduction of methyl groups into compounds **0–3**, shown below, leads to unusual reactivities towards base-catalysed cyclization in the most heavily substituted esters **3**: these include both a change of mechanism and the loss of the acceleration due to the *gem*-dimethyl effect.[2] This prompted a study of the NH-acidity of these compounds as a measure of the nucleophilicity of the ureido groups in this series of ureidoesters.



MUE, R^1 = Me
PUE, R^1 = Ph

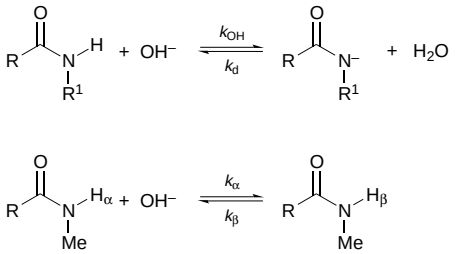


MH, R^1 = Me
PH, R^1 = Ph

	R^2	R^3	R^4
0-MUE	H	H	H
1-MUE	Me	H	H
2-MUE	Me	Me	H
3-MUE	Me	Me	Me
1-PUE	Me	H	H
3-PUE	Me	Me	Me

Rates of base-catalysed hydrogen exchange were measured by means of dynamic NMR. The collapse of the methyl doublet due to the NH–CH_3 coupling in the ω-methyl hydantoates and the broadening of the NH peak of the ω-phenyl esters with changing pH were monitored in buffers.

These exchange phenomena are due to the processes shown in Scheme 1.



Scheme 1

Pseudo-first-order rates of hydrogen exchange, k_{exch}, were obtained as described in the Experimental section. In the pH region where exchange phenomena could be observed, spectra had to be recorded rapidly as cyclization to hydantoin is a competing reaction. To calculate the second-order rates, $k_{OH} = k_{exch}/a_{OH}$, a_{OH} was taken as antilog (pH -14), where pH is the glass-electrode value measured in the buffer containing the correct amount of acetonitrile. The acidity constant was obtained as

$$K_{NH} = \frac{k_{OH}}{k_d} K_w$$

with k_d, the diffusion-controlled rate for the protonation of the ureide anion, being taken as 10^{10} dm^3 s^{-1} mol^{-1} and K_w, the ionic product of water, as 10^{-14}. Because of poor solubility, spectra had to be run in 5:1 (v/v) water–acetonitrile. In this solvent mixture pK_w is little different from that of pure water [14.33 in 20% (w/w) MeCN at 25 °C][3] and, in view of the remaining uncertainties, refinements were considered unwarranted. **3**-PUE is still less soluble and 50% aqueous MeCN was used. In this medium pK_w differs considerably[3] from 14 and the respective pK values were calculated as above only for the sake of comparison.

As far as the ring-closure reaction is concerned, the results in Table 1 show that differences in reactivity between compounds **1** and **3**, in both the MUE and PUE series, cannot be attributed to the different basicity of the ureide anions. **2**-MUE, with one methyl group at the 2 position, is considerably less acidic than **1**-MUE, with no methyl group. This is not likely to be simply an inductive effect; in a *Z*-conformation on the ester side of the urea molecule, an extra methyl group can be expected to hinder the solvation of the negatively charged oxygen in the anion. The reversal of this trend in compounds **3** is most likely due to a steric effect: strain relieved by twisting the dialkylamino group out-of-plane diminishing amide conjugation. This should make the NH proton more acidic because of increased conjugation within the secondary amide group. Strong acidifying effects upon *N*-methyl substitution of secondary acylureas have been observed.[4]

The less heavily substituted ethyl hydantoates have been prepared by Kaválek and Štérba.[5] Esters **2** and **3**, however, cyclized rapidly in the presence of moisture and had to be prepared under strictly anhydrous conditions, as described in the Experimental section.

Experimental

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Bruker WM-250 instrument. pH Values were measured with a Radiometer pH M 84 Research pH-meter using a GK 2401 C electrode.

Materials.—Inorganic reagents and buffer components were of analytical-reagent grade and used without further purification. Buffer solutions were prepared with CO_2-free water, to 0.03 M total

Table 1 Rates of base-catalysed hydrogen exchange in ethyl hydantoates and pK_{NH} estimates in 5:1 (v/v) water–acetonitrile at 19 °C

Compound	pH	k_{exch}/s^{-1}	k_{OH}/dm^3 s^{-1} mol^{-1}	pK
In 5:1 (v/v) water–acetonitrile				
0-MUE[a]	9.84	12	1.7×10^5	18.8
1-MUE	9.43	4.0	1.6×10^5	18.8
	9.84	11.5		
2-MUE	10.21	5.5	3.6×10^4	19.45
	10.45	11		
3-MUE	9.43	2.5	9.3×10^4	19.0
1-PUE	6.90	6.3	7.9×10^7	16.1
	7.19	12.2		
In 1:1 (v/v) water–acetonitrile				
1-PUE	7.44	4.5	1.6×10^7	16.8
3-PUE	7.44	5.8	2.1×10^7	16.7

[a]For 3-NH we obtained $k_{OH} = 1.3 \times 10^6$ dm^3 s^{-1} mol^{-1}, pK = 17.9.

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†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1997, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.
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Table 2 ^{1}H NMR spectra of ureido esters and hydantoins in 5:1 (v/v) water–acetonitrile [HD_2CCN (δ 1.94) as reference, splittings in Hz in parentheses]

Compounds	1-Me	2-H	2-Me	3-Me	5-H	5-Me	OCH_2Me	OCH_2*Me*
MUE and PUE[a]								
0-MUE		3.780d (6.1)				2.553d (4.6)	4.092q (7.2)	1.149t (7.2)
1-MUE		3.955s		2.805s		2.595d (4.5)	4.095q (7.2)	1.152t (7.2)
2-MUE		4.073q (7.1)	1.266d (7.1)	2.691s		2.596d (4.4)	4.073q (7.1)	1.141t (7.2)
3-MUE			1.261s	2.706s		2.550d (4.5)	4.034q (7.2)	1.133t (7.1)
1-PUE		4.032s		2.967s			4.111q (7.2)	1.156t (7.2)
3-PUE[c,d]			1.327s	2.913				1.122 (7.2)
MH and PH[b]				2.834	3.917s			
0-MH	2.836s			2.836s	3.910s			
1-MH	2.738s			2.811s	3.973q (7.0)	1.278d (7.0)		
2-MH	2.757s			2.853s		1.257s		
3-MH	2.929s				4.100s			
1-PH[e]	2.862s					1.408s		
3-PH[c]								

[a]See formulae for numbering in esters and hydantoins. [b]δ 5-Ph: *o*-H 7.185, *m*-H 7.266, *p*-H 7.064; NH 8.03. [c]In 50% H_2O–CD_3CN v/v. [d]δ(NH) 7.98. [e]δ (3-Ph) 7.25m (3 H), 7.47m (2 H).

concentration, and the ionic strength was adjusted with KCl to 0.1 M. CD_3CN was 99% from Aldrich.

Ethyl Hydantoates.—*General procedure.* A slight excess (8%) of methyl or phenyl isocyanate was added to the freshly distilled amino ester (5 mmol) in dry benzene (5 ml) under ice cooling. The mixture was stirred for 15 min at 0 °C and then for 1 h at room temperature. Where the products precipitated they were filtered off and washed with dry benzene and hexane, otherwise the reaction mixture was evaporated to dryness and the solids recrystallized from dry benzene. The yields of pure esters were 86–96%.

Compounds **0**-MUE, **1**-MUE and **1**-PUE were prepared by the above procedure and were identified by comparison with the mps and NMR parameters described in ref. 4.

Ethyl 2,3-*dimethyl*-5-*phenylhydantoate* (**2**-PUE) had mp 95–96.5 °C; δ_H ($CDCl_3$) 1.27 (t, 3 H, *Me*CH_2OCO), 1.45 (d, 3 H, *Me*CH), 2.98 (s, 3 H, MeN), 4.19 (q, 2 H, CH_2OCO), 5.09 (q, 1 H, C*H*NMe), 6.54 (s, 1 H, HNPh), 7.03–7.38 (m, 5 H, Ph) (Found: C, 62.51; H, 7.48; N, 11.14. $C_{13}H_{18}N_2O_3$ requires C, 62.38; H, 7.25; N, 11.19%).

Ethyl 2,2,3-*trimethyl*-5-*phenylhydantoate* (**3**-PUE) had mp 108.5–110 °C; δ_H ($CDCl_3$) 1.23 (t, 3 H, *Me*CH_2OCO), 1.43 (s, 6 H, *Me*$_2$CH), 3.00 (s, 3 H, CH_3N), 4.18 (q, 2 H, CH_2OCO), 6.33 (s, 1 H, HNPh), 7.01–7.36 (m, 5 H, Ph) (Found: C, 63.55; H, 7.51; N, 10.87. $C_{14}H_{20}N_2O_3$ requires C, 63.61; H, 7.62; N, 10.60%).

Hydantoates **2**-MUE and **3**-MUE were obtained *in situ* as described below.

Dynamic NMR.—The ready cyclization of the ureido esters limited the time and the pH region (below 7 for PUE and below 10.5 for MUE) available for recording the spectra. Table 2 lists the NMR parameters for the esters and the product hydantoins. The final solutions were prepared by mixing 0.4 ml of the aqueous buffer (formate, acetate, phosphate, borate or carbonate) with 0.1 ml of an ester CD_3CN solution (0.1 g in 1 ml). Esters **2**-MUE and **3**-MUE were prepared *in situ* by mixing equal amounts of 10^{-3} M solutions of the respective amino ester and of methyl isocyanate in CD_3CN just before recording the spectra. In the case of MUE, spectra for the 5-Me doublet could be taken before and after coalescence in solutions of various pH. The relaxation time, T_2, in each spectrum was determined from the band width at half intensity of the 3-methyl signal. For **0**-MUE one of the lines of the ethoxymethyl group was used, adding the difference of this line and a line of the 5-Me signal at slow exchange. Estimates of $k_{exch} = k = k_\alpha + k_\beta$ were obtained by means of approximate solutions;[6] line-intensity methods for cases with slow[7] and fast[8] exchange were preferred. The values for the rate constants were then refined by means of complete line-shape-analysis simulations.[9] In the case of PUE, line-broadening of the NH signal was monitored: $k_{exch} = \pi(W^* - W^0)$, where W^* is the line-width of the exchange-broadened signal and W^0 the width in the absence of observable exchange. Following the recommendations of Perrin *et al*.,[10] instrument inhomogeneity was compensated for by subtracting the width of a line of the ester methyl triplet from every NH line width.

We thank the National Foundation for Scientific Research of Bulgaria for funding this research and the Bulgarian Academy of Sciences and The Royal Society for travel funds. We thank also Dr N. Vassilev for help with the CLSA program.

Received, 24th December 1996; Accepted, 28th February 1997
Paper E/6/08619E

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