Alkaline Hydrolysis of Hydantoin, 3-Methylhydantoin, and 1-Acetyl-3-methylurea. Effect of Ring Size on the Cleavage of Acylureas

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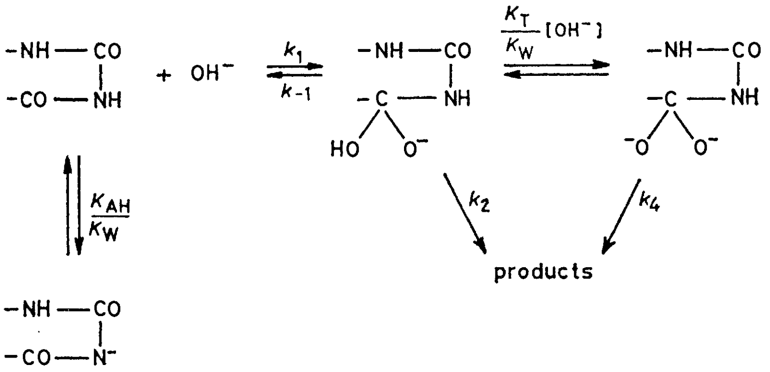
The alkaline hydrolysis of hydantoin, 3-methylhydantoin, and 1-acetyl-3-methylurea was found to be mainly second order in OH^- at low basicity changing over to first order at higher values. The reaction proceeds by attack of OH^- on the un-ionized substrate with rate-limiting base catalysed breakdown of the tetrahedral intermediate. At high hydroxide ion concentrations the breakdown becomes fast and addition determines the rate. Some interpretations of hydrolysis of hydantoin derivatives have been revised. The effect of ring size on the pK values for deprotonation at the imide nitrogen and on the rates of formation and breakdown of the tetrahedral intermediate has been examined for the five- and six-membered ring acylureas and the open-chain compound. The acidity decreases strongly in this order. The enhanced acidity of the five-membered ring acylureas is further exhibited in the pK value of 13.06 for ionization at N-1 of 3-methylhydantoin. The $k^6 : k^5$ ratio for formation of the tetrahedral intermediate is uniformly *ca.* 2—3, while for the partitioning ratio for its breakdown, $k^6 : k^5$ is different for the unsubstituted and *N*-methylated compounds, 0.08 and 1.6, respectively. The open-chain compound adds OH^- an order of magnitude more slowly than the cyclic derivatives. The nature of the effects is discussed.

In 1922, Ingold *et al.*[1] published an important paper on the *gem*-dimethyl effect based on the rates of alkaline hydrolysis of hydantoins. Subsequently, two detailed kinetic investigations on the mechanism of hydrolysis of hydantoin derivatives have been reported. Ivin *et al.* have studied the rearrangement of 5-carboxymethylidenehydantoins to orotic acids, the slow stage of which is the hydrolysis of the hydantoin ring.[2a] From rate profiles [2b,c] and ample additional evidence,[2d-f] these authors concluded that two parallel reactions take place: attack of OH^- on the free hydantoin ring and on its N-3 anion. For the hydrolysis of the hydantoin ring of allantoin, Vogels *at al.*[3] observed these two reactions below pH 8 and above 13, respectively, but were unable to explain a reaction second order in OH^- and a plateau in the intermediate region. Similar rate profiles in the case of the six-membered ring system, dihydrouracil (4) and some derivatives, have been convincingly inter-



(1)

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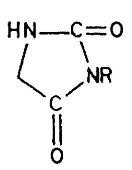
[1] C. K. Ingold, S. Sako, and J. F. Thorpe, *J. Chem. Soc.*, 1922, 1177.

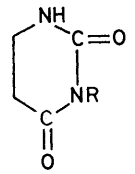
[2] (*a*) B. A. Ivin, G. V. Rutkovskii, E. G. Sochilin, and I. Yu. Tsereteli, *Zhur. org. Khim.*, 1972, **8**, 840; (*b*) B. A. Ivin, G. V. Rutkovskii, and E. G. Sochilin, *ibid.*, p. 1951; (*c*) B. A. Ivin, G. V. Rutkovskii, T. N. Rusavskaya, and E. G. Sochilin, *ibid.*, 1975, **11**, 2188; (*d*) B. A. Ivin, G. V. Rutkovskii, and E. G. Sochilin, *ibid.*, 1973, **9**, 179; B. A. Ivin, G. V. Rutkovskii, S. A. Andreev, and E. G. Sochilin, *ibid.*, (*e*) p. 420; (*f*) p. 2194.

[3] G. D. Vogels, F. E. de Windt, and W. Bassi, *Rec. Trav. chim.*, 1969, **88**, 940.

preted[4,5] by reaction only with the un-ionized substrate in terms of a mechanism involving slow breakdown of the tetrahedral intermediate as mono- and di-anion changing to rate-limiting formation at high basicity.



(1) R = H
(2) R = Me



(4) R = H
(5) R = Me

$CH_3CONHCONHCH_3$
(3)

We now report a study of the five-membered ring system, hydantoin (1) and 3-methylhydantoin (2), and of the open-chain compound, 1-acetyl-3-methylurea (3), undertaken to establish the general validity of the mechanism of equation (1). A further point of interest was that the rate profile observed for dihydrouracil and presumably for hydantoin permits direct estimation of k_1, the rate constant for formation of the tetrahedral intermediate, and k_2/k_{-1} and $k_4K_T/k_{-1}K_W$, the rate constant ratios for partitioning to reagents and products *via* the two pathways of equation (1). The effect of ring size upon opening of cyclic carboxy derivatives has been examined without direct evidence on the relative importance of the formation and breakdown of the tetrahedral intermediate as only the overall rate could be measured. A recent study of *N*-phenyl-lactams,[6] where knowledge of the kinetic behaviour of anilides upon hydrolysis permits a more direct assignment of the rate-determining step, has left the case of five- and six-membered rings equivocal because of the ambiguity stemming from a rate profile uniformly first order in OH^- and the absence of sufficient supplementary evidence.

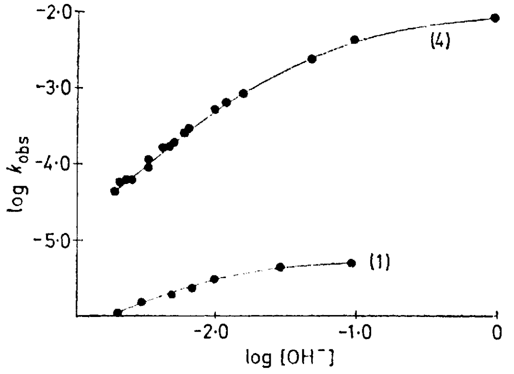


FIGURE 1 Rate profiles for hydrolysis at 25 °C and I 1M (KCl) of hydantoin (1) in NaOH and dihydrouracil (4) in KOH (data of Sander). The lines are theoretical curves obtained with the constants of Table 2

RESULTS

The dependence of the rate of alkaline hydrolysis of hydantoin, 3-methylhydantoin, and 1-acetyl-3-methylurea upon the hydroxide ion concentration is shown on Figures 1 and 2. In the case of hydantoin, the slope in the logarithmic plot decreases from 0.7 to 0 indicating a change from apparent first to zero order. The ionization of hydantoin at N-3 occurs with a pK value of 9.04 and no second ionization could be detected in the u.v.-spectra up to 1M-KOH. The slopes of the plots for 3-methylhydantoin and the urea (3) decrease from 2—1.5 to near 0 indicating the incursion of an ionization with a pK value of *ca.* 13. This could be detected by changes in the u.v. spectra and the spectrophotometrically determined pK values are listed on Table 1. 3-Methyldihydrouracil (5) does not ionize in this region;[4] however, ionization of 3-methylhydantoin at N-1 is not entirely unexpected as 3-phenylhydantoin was found[7a,b] to have a pK value of 12.52. For the open-chain compound there is little doubt that ionization occurs at the nitrogen atom between the two carbonyl groups.

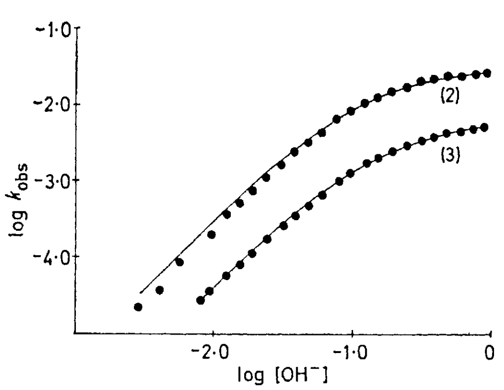


FIGURE 2 Rate profiles for hydrolysis of 3-methylhydantoin (2) and 1-acetyl-3-methylurea (3) at 25 °C and I 1M (KCl) in KOH solutions. The lines are theoretical curves obtained with the constants of Table 2

TABLE 1

Comparison of acid dissociation constants of acylureas and imides

Compound	pK_{AH}	Compound	pK_{AH}
(3) [a]	13.15 ± 0.04	Diacetylamine [c]	12.9
(4) [b]	11.66	Glutarimide [c]	11.5
(1) [a]	9.04 ± 0.05	Succinimide [c]	9.5
(2) [a]	13.06 ± 0.05		

[a] Present work, 25 °C, I 1M (KCl). [b] Ref. 4, 25 °C, I 1M (KCl). [c] Ref. 12.

$$k_{obs} = \frac{1}{1 + \frac{K_{AH}}{K_W}[OH^-]} \times \frac{k_1k_2[OH^-] + k_1k_3[OH^-]^2}{k_{-1} + k_2 + k_3[OH]} \qquad (2)$$

The steady-state solution for the reaction sequence of equation (1) gives (2) where k_3 stands for k_4K_T/K_W.

In the range of basicity studied there was no apparent

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[4] E. G. Sander, *J. Amer. Chem. Soc.*, 1969, **91**, 3629.

[5] I. Blagoeva, B. J. Kurtev, and I. G. Pojarlieff, *J. Chem. Soc.* (*B*), 1970, 232.

[6] G. M. Blackburn and J. D. Plackett, *J.C.S. Perkin II*, 1972, 1366.

[7] (*a*) I. B. Blagoeva and I. G. Pojarlieff, *Compt. rend. Acad. bulg. Sci.*, 1977, **30**, 1043; (*b*) M. Bergon and J.-P. Calmon, *Compt. rend.*, 1976, **283C**, 637.

effect of the $k_1k_2[OH^-]/k_{-1}$ term which is probably swamped by the second-order OH^- reaction. The values of k_1 and k_3/k_{-1} were at first estimated from the linear form (3) of

$$[OH^-] = -\frac{k_{-1}}{k_3} + k_1\frac{[OH^-]^2}{k_{corr}} \qquad (3)$$

equation (2) neglecting k_1k_2 and k_2. k_{corr} in equation (3) is the observed rate constant corrected for ionization. Data were used from those parts of the plots of $\log k_{corr}$ against $\log[OH^-]$ where the slope is intermediate between 1 and 2.

As we were interested in comparing six- *versus* five-membered ring reactivities we recalculated the rate constants for dihydrouracil from experimental data kindly supplied by Dr Sander. The need for this arose since his published values for k_1k_2/k_{-1} and k_1k_3/k_{-1} were obtained without correcting for ionization.[4] Directly determined values of K_{AH}/K_W for compounds (2) and (3) were used in the calculations; in the case of (1) and (4), the apparent acidity constants in 1M-KCl were divided by a K_W value of 1×10^{-14}.

The k_1 and k_3/k_{-1} values obtained did not give a very good fit for the entire curves. In order to refine this, the experimental data were subjected to an iterative procedure seeking the values of k_1, k_2/k_{-1}, and k_3/k_{-1} giving the best fit to equation (2). The first attempts, carried out without weighting factors, gave large errors for k_3/k_{-1}, small but negative values for k_2/k_{-1}, and the fit for the bottom part of the curve was poor. This was apparently due to the predominance of datum points having large amplitudes. Different ways to weight the datum points were tried and it was found most appropriate to make the weighting factors inversely proportional to the amplitude of each datum point. An improved fit of the entire curve and smaller errors for the constants were obtained but the values of k_2/k_{-1} were again negative. Arbitrary input values of the constants resulted in the same solution. The negative value of k_2/k_{-1} (albeit small in magnitude) is probably due to some systematic error common to our and Sander's experiments. Attempts to estimate k_2/k_{-1} from the bottom part of the curves were unsatisfactory and only the highest limit of k_2/k_{-1} was taken [except in the case of compound (3) where the results were consistent with the entire curve]. In the final minimization, k_2/k_{-1} was assumed to be zero and the values thus obtained are listed on Table 2. The latter are practically the same as those obtained from iteration of the entire curve.

TABLE 2

Rate parameters of formation and partitioning of the tetrahedral intermediate for alkaline hydrolysis of acylureas at 25 °C and ionic strength 1M (KCl)

Compound	k_1/dm^3 mol^{-1} s^{-1}	k_2/k_{-1}	k_3/k_{-1}/ dm^3 mol^{-1}
(1)	0.495 ± 0.007	$<1 \times 10^{-2}$	120 ± 19.7
(2)	0.297 ± 0.007	$<1 \times 10^{-2}$	10.2 ± 0.83
(4) [a]	1.83 ± 0.009	$<1 \times 10^{-4}$	9.44 ± 0.37
(5) [b]	0.717	2.46×10^{-2}	16.7
(3)	0.0488 ± 0.0006	$(1.08 \pm 0.83) \times 10^{-2}$	8.23 ± 0.49

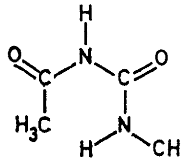
[a] See text. [b] Ref. 4.

DISCUSSION

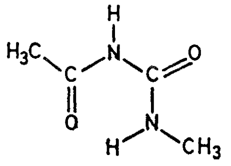
Mechanism of Hydantoin Hydrolysis.—First-order dependence on OH^- at pH values where the substrate is completely ionized is usually interpreted as reaction of OH^- on the anion. As already mentioned, this is the mechanism assumed by Ivin and his co-workers for the hydrolysis of 5-carboxymethylidenehydantoin, which is actually a reaction of a dianion taking the ionization of CO_2H into account.[2b] They supported their assumption with data from ionic strength and solvent effects,[2d] activation parameters in water and isodielectric media,[2c] and the effects of ion aggregation.[2f] Furthermore, various α-substituted 5-carboxymethylidenehydantoins, together with hydantoin-5-yl acetic acid, were found to give an isokinetic series so the conclusion was drawn that all compounds of the series react by this mechanism.[2c] These proofs, however, are irrelevant for choosing between attack of OH^- on the dianion of 5-carboxymethylidenehydantoin and the mechanism of equation (1) in the region of the kinetically indistinguishable second-order OH^- attack on the respective monoanion. In both cases, with the substrate being completely ionized as the dianion, the ground and the transition state will be of the same charge and the same effects will be predicted. Evidence that the mechanism of equation (1) provides lower barriers on the path from reactants to products can be obtained from the complete rate profiles. For hydantoin studied under conditions of complete ionization, the apparent first order reaction changes to zero with no second ionization to produce an unreactive species. The only plausible explanation is the change in the rate-limiting step when $k_3[OH^-]$ in the denominator of equation (2) becomes larger than $k_{-1} + k_2$. Further evidence is provided by the less acidic compounds, 3-methylhydantoin and 1-acetyl-3-methylurea, which show second order OH^- reactions at pH values much below their first pK, thus indicating catalysis by a second hydroxide ion. The change to zero order at higher basicity is readily understood by the combined effect of ionization to the unreactive anion and the change of the rate-limiting step. Similar evidence is contained in the work of Ivin *et al.* The case of 5-carboxymethylidenehydantoin [2b] is equivocal as the slope of the logarithmic plot changes abruptly from +1 to −1 at *ca.* 6M-KOH which could be due to a simultaneous change of the rate-limiting step and the observed ionization to the trianion (pK 15.17), but could be attributed as well, as the authors do, to the differences in the acidity functions which the ionization and the rate follow. With the α-nitro derivative studied later [2c] the case is unambiguous since the change of slope from +1 to −1 occurs at *ca.* 0.1M-KOH where $[OH^-]$, a_{OH^-}, and any acidity function differ by little and can in no case account for the observation. Hydantoin-5-ylacetic acid is also a clear cut case as the slope changes to zero at 0.2—0.3M-KOH where ionization to the trianion is highly unlikely taking into account the above quoted pK for ionization at N-1 of the more acidic 5-carboxymethylidene compound. The mechanism of equation (1) also explains the rate profile for allantoin hydrolysis from pH 9 to 13 as a changeover from rate-limiting breakdown ($k_1k_3[OH^-]^2/k_{-1}$) to formation ($k_1[OH^-]$) of the tetrahedral intermediate followed by reaction of the anion at pH values >13.

The rate profiles of hydantoin, 3-methylhydantoin, and 1-acetyl-3-methylurea are very similar to those of dihydrouracil derivatives.[4,5] As the leaving group is the same, there can be little doubt that they are hydrolysed by the same mechanism. The $k_{D_2O} : k_{H_2O}$ ratio >1 for k_3/k_{-1} found in the case of 3-methyldihydrouracil[4] is a strong indication, from what is known of anilide hydrolysis, that the breakdown of the tetrahedral intermediate takes place with slow rupture of the C–N bond accompanied by accumulation of negative charge on nitrogen, *i.e.* the mechanism assumed for anilides with strong electron-withdrawing groups.[8] The analogy with *p*-nitroanilides, in particular, is reinforced by the similarity of the pK_{BH^+} value for the two leaving groups, *p*-nitroaniline, 1.02, and urea, −0.30, although the difference in chemical nature restricts such a conclusion.

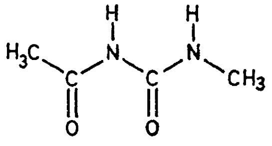
Effect of Ring Size.—Considering the reactivities upon hydrolysis of the three types of compounds, dihydrouracils, hydantoins and the open-chain acylurea the following factors appear important: angle strain and bond opposition in the ring systems and conformation of the open-chain derivative. Examination of models and *X*-ray data for allantoin[9] and dihydrouracil[10] show that there is considerable angle deformation in the five-membered ring. According to the *X*-ray data, the NH·CO·NH·CO moiety is essentially planar in the cyclic compounds. An i.r. spectral study[11] of acylureas suggests the *Z,E*-conformation as the preferred one in dilute CCl_4 [formula (B)].



(A)



(B)



(C)

Some of the properties of the compounds are demonstrated by the p*K* values for the ionization at the nitrogen. The values listed in Table 1 show that these are remarkably similar to those of the respective imides. Edward and Terry[12] explained the differences in the p*K* values of the imides by mutual repulsion of the negative charges on the carbonyl oxygen atoms in the anion of diacetylamine in the *Z,Z*-conformation [equivalent to formula (C)] and by lack of planarity of the six-membered ring. At present there is evidence from dipole moments and i.r. spectra[13] that the preferred conformation of diacetylamine is the *Z,E*-one. In this conformation the carbonyl oxygen atoms are also closer to each other than in the *E,E*-conformation of the cyclic compounds, 4.1 and 4.7 Å from Dreiding models. However, estimates of the electrostatic repulsions arising in the anion can account for only part of the 1.5 p*K* units difference between open-chain and six-membered ring compounds, imides and acylureas alike. Noteworthy is the difference in $\lambda_{max.}$ of the anions of acylurea (3) and dihydrouracil (Table 3) suggesting better conjugation in the latter.

TABLE 3

Properties of compounds

Compound	M.p. (°C)	Lit. m.p. (°C)	Analytical λ/nm	$\lambda_{max.}$/nm of anions
(1)	217—218	220 [a]	227	227
(2)	181.5—182.5	181—182 [b]	230	228
(3)	178—179	180 [c]	230	224
(4)				232

[a] C. Harries and M. Weiss, *Annalen*, 1903, **327**, 355. [b] Ref. 21. [c] Ref. 22.

The increased acidity of succinimide has been attributed to ring strain by Barlin and Perrin.[14] The decrease of ring bond angles will increase the *s* character of the N–H bond which probably accounts for the rather large effect. The enhanced tendency of 3-substituted hydantoins to ionize at N-1 was already mentioned.

When the actual rates of hydrolysis of the acylureas under consideration are compared, hydantoin is hydrolysed one or two orders of magnitude more slowly since due to its high acidity, the concentration of un-ionized molecules is very low. When ionization is taken into account, the rate is determined by k_1k_3/k_{-1} at the lower basicities studied and at the higher values by k_1. In the former case the order of reactivities is different for the unsubstituted and 3-methyl-substituted compounds (Table 2). For k_1, the bimolecular rate constant for formation of the tetrahedral intermediate, the effect of ring size is uniform: hydantoin and 3-methylhydantoin add OH^- 2—3 times more slowly than the six-membered analogues. The same is true of the 3-phenyl derivatives[7a] shown to hydrolyse with rate-determining k_1 where $k^6 : k^5$ was *ca.* 3. This is in accord with the Brown–Brewster–Schechter rule.[15] With lactones where k_1 is assumed to be important, the $k^6 : k^5$ ratio ranges from 173 for acid to 20—30 for alkaline hydrolysis.[16]

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[8] L. D. Kershner and R. L. Schowen, *J. Amer. Chem. Soc.*, 1971, **93**, 2014.

[9] D. Mootz, *Acta Cryst.*, 1965, **19**, 726.

[10] D. C. Rohrer and M. Sundaralingam, *Acta Cryst.*, 1960, **26B**, 546.

[11] C. I. Jose and P. R. Pabrai, *Indian J. Chem.*, 1969, **7**, 594.

[12] J. T. Edward and K. A. Terry, *J. Chem. Soc.*, 1957, 3527.

[13] C. M. Lee and W. D. Kumler, *J. Amer. Chem. Soc.*, 1962, **84**, 571.

[14] G. B. Barlin and D. D. Perrin, *Quart. Rev.*, 1966, **20**, 75.

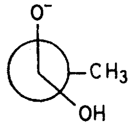
[15] H. C. Brown, J. H. Brewster, and H. Schechter, *J. Amer. Chem. Soc.*, 1954, **76**, 467.

[16] T. C. Bruice and U. K. Pandit, *J. Amer. Chem. Soc.*, 1960, **82**, 5862.

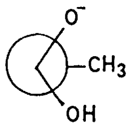
The smaller differences for acylureas are probably due to two reasons. Dihydrouracil is a 'flattened' ring system and the tetrahedral intermediate will not be fully devoid of bond opposition. Further, the negative charge of the tetrahedral intermediate will be stabilized by the adjacent nitrogen atom N-1 in the five-membered rings. With the open-chain derivative (3), k_1 is considerably smaller probably because of a less strained ground state.

Only the second-order OH^- terms, k_3/k_{-1}, for the breakdown of the tetrahedral intermediate could be determined. This is a complex constant equal to k_4K_T/K_Wk_{-1}. We shall limit our discussion only to effects which appear as dominant. Electron withdrawal at the acyl part of the molecule is known from anilide hydrolysis[17] to enhance k_3/k_{-1} which is in accord with the >10-fold value of k_3/k_{-1} for hydantoin compared with dihydrouracil. The value of k_3/k_{-1} for allantoin estimated from the data of Vogels *et al.*[3] is 2 000 $dm^3\ mol^{-1}$. For hydantoin the larger k_3/k_{-1} is probably due in part to release of bond angle strain in the k_4 step. Some support to this suggestion is lent by the similarity of k_3/k_{-1} for 1-acetyl-3-methylurea and dihydrouracil, the tetrahedral intermediates of which should be free of bond angle strain.

The reversal of reactivities of the *N*-methyl derivatives is of considerable interest. The methyl group increases k_3/k_{-1} specifically in the six-membered ring, but decreases it in the five-membered one. Such an effect can only be of steric origin. The *N*-methyl group can be envisaged to give rise to greater strain in the tetrahedral intermediate of dihydrouracil for two reasons. (a) The methyl group will oppose the equatorial oxygen in dihydrouracil but lie between the two oxygens in hydantoin; a probably exaggerated presentation is given by the formulae (D) and (E). (b) The smaller endocyclic bond angles in the five-membered ring shift the methyl group away from the neighbouring oxygens.



(D)



(E)

In order for such a strain to accelerate the reaction it should be best relieved by rupture of the C–N (k_4) rather than the C–O bond (k_{-1}). This should be the case as the unstrained axial oxygen in dihydrouracil has the right geometry for leaving.[18]

For such an explanation to be true requires that the general effect of *N*-methyl substitution is to decrease strongly k_3/k_{-1} compared with that for the NH compounds. This tendency has been claimed[19] in the case of *p*-nitroanilides although not very convincingly as it is based on the non-observance of k_3/k_{-1}. If the inversal of the $(k_3/k_{-1})^5 : (k_3/k_{-1})^6$ ratio upon methylation is really due to the eclipsing of CH_3 and the equatorial oxygen in the six-membered ring then this effect should also occur in the $(k_2/k_{-1})^5 : (k_2/k_{-1})^6$ ratio. Some support is lent to this by comparison of the $k^5 : k^6$ ratio for succinimide and glutarimide and their *N*-methyl derivatives which presumably are hydrolysed with observed rates determined by k_1k_2/k_{-1}. The former ratio[12] is 5 against 0.08 for the *N*-methyl case.[20] The $k^5 : k^6$ ratios for k_1k_3/k_{-1} are 3.4 and 0.25 for the unsubstituted and methylated acylureas, respectively.

EXPERIMENTAL

Materials.—All compounds were prepared by standard procedures. Hydantoin was obtained by evaporating a solution of hydantoic acid in 5N-HCl to dryness on a boiling water-bath. 3-Methylhydantoin was prepared from hydantoin and methyl iodide in an alcoholic solution of KOH.[21] 1-Acetyl-3-methylurea was obtained by the Hofmann degradation of acetamide.[22] All compounds were recrystallized from water to constant m.p.s.

The carbonate-free solutions of sodium or potassium hydroxide were kept under nitrogen in automatic burettes. Commercial KCl was purified by two crystallizations from 0.1N-HCl.[23]

Rate Measurements.—The rates were followed spectrophotometrically by the disappearance of the substrates. The products of hydrolysis have no measurable absorption above 225 nm. The analytical wavelengths (Table 3) were chosen so that the absorbance of the most concentrated hydroxide solutions did not exceed 0.2 in a 1 cm cell. The Lambert–Beer law is obeyed in the concentration region used. Hydroxide solution (3 ml) (*I* 1M with KCl) was equilibrated for 15 min in the thermostatted cells (25.0 ± 0.1 °C) of a Unicam SP 800 spectrophotometer and then a solution (10—25 μl) of the substrate was added so that the final concentration was 1×10^{-4}—1×10^{-3}M. Care was taken that at least a 10-fold excess of the base was present. In the case of hydantoin only, hydrolysis was carried out in sealed tubes and the absorbance measured immediately after taking the tubes out of the temperature-controlled bath without quenching the reaction. Good linear plots of log *A* against time were obtained from which the rate constants were calculated by least squares treatment. Averages of 2—3 runs were taken, the deviation being $\leqslant 5\%$.

Iteration Procedure for Adjustment of Kinetic Parameters.—The procedure is based on the classical least squares method using the integral parameter sensitivities described previously.[24] The program written in BASIC was adapted to find the best fit to equation (2) of the parameters k_1, k_2/k_{-1}, and k_3/k_{-1}. Calculations were carried out on a Wang 2200B minicomputer.*

p*K Measurements.*—The pK_{AH} value of hydantoin at 25.0 ± 0.05 °C and *I* 1M (KCl) was obtained by titration

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* A copy of the program is available on request.

[17] R. H. DeWolfe and R. C. Newcomb, *J. Org. Chem.*, 1971, **36**, 3870.

[18] P. Deslongchamps, *Tetrahedron*, 1975, **31**, 2463.

[19] A.-M. Segretain, M. Beugelmans-Verrier, and M. Laloi-Diard, *Bull. Soc. chim. France*, 1972, 3367.

[20] H. K. Hall, M. K. Brandt, and R. M. Mason, *J. Amer. Chem. Soc.*, 1958, **80**, 6420.

[21] L. Siemonsen, *Annalen*, 1904, **333**, 101.

[22] A. W. Hofmann, *Ber.*, 1881, **14**, 2735.

[23] S. O. Eriksson and C. Holst, *Acta Chem. Scand.*, 1966, **20**, 1892.

[24] V. S. Dimitrov, *J. Magnetic Resonance*, 1976, **12**, 71.

under nitrogen of a 5 × 10^{-3} M solution of hydantoin with a 0.109M solution of tetramethyl ammonium hydroxide using a Radiometer 26 pH-meter. The error quoted in Table 1 is the spread of the data. The pK values of 3-methylhydantoin and 1-acetyl-3-methylurea were determined spectrophotometrically at 230 nm in potassium hydroxide solutions adjusted to 1M with KCl at 25.0 ± 0.1 °C. The absorbance of the free molecules was measured in water. Because of rapid hydrolysis, the absorbance at a given concentration of OH^- was obtained by extrapolating to time zero plots of log$A$ against time. Averages of two determinations were taken. The absorbance of the anion

$$A = A_{A^-} - \frac{K_W}{K_{AH}} \times \frac{A - A_{AH}}{[OH^-]} \qquad (4)$$

was treated as unknown and K_{AH} was obtained from a least squares fit of equation (4).

Product Analysis.—Hydantoins are well known to give hydantoic acids as the first products upon alkaline hydrolysis.[1,25] That the same type of cleavage occurs with 1-acetyl-3-methylurea yielding acetic acid and *N*-methylurea was checked as follows. 1-Acetyl-3-methylurea (0.1 g) was hydrolysed in 1M-potassium hydroxide (10 ml) at 25 °C for 1 h. Three reference compounds were separated by t.l.c. on silica, 1-acetyl-3-methylurea, *N*-methylurea, and acetamide. The first two are separated by methanol–chloroform (2 : 1) and the last two by methanol–chloroform (1 : 2) as eluants. Only methylurea could be detected in the hydrolysate. No ammonia could be detected with Nessler's reagent in the alkaline solution before neutralization.

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[25] E. Ware, *Chem. Rev.*, 1950, **46**, 403.