Hydrolysis of Ureas. Kinetics and Mechanism of the Basic Hydrolysis of Indole-1-carboxamides and (5*H*-Dibenz[*b*,*f*]azepine)-5-carboxamide

Paolo Linda*

Istituto di Chimica, Università di Trieste
Italy

Cynthia Ebert, Mara Lovrecich and Fulvio Rubessa
Istituto di Chimica Farmaceutica, Università di Trieste,
Italy

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The hydroxide ion catalyzed hydrolysis of indole-1-carboxamide and indole-1-(*N*,*N*-dimethyl)carboxamide has been studied in water at 60.0° and [OH^-] concentration between 0.3-2.4*N*. The rate constants of formation of the tetrahedral intermediate are strongly increased by *N*-substitution with a heteroaromatic ring in comparison with simple amides. Carbamazepine, (5*H*-dibenz[*b*,*f*]azepine)-5-carboxamide, a potent anticonvulsant drug, is particularly stable under these conditions.

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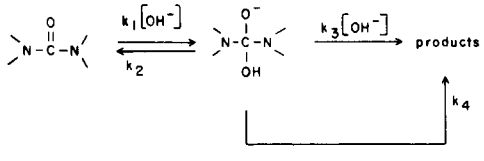
The kinetics of hydrolysis in basic media of urea I [1] and *N*,*N*,*N'*,*N'*-tetramethylurea (II) [2] has been previously studied. The apparent order in hydroxide ion concentration was found between 1 and 2. The presence of a second-order term in hydroxide ion suggested that the rate determining step under these conditions is the hydroxide catalyzed breakdown of the tetrahedral intermediate formed by the addition of hydroxide ion to the substrate in a fast equilibrium. Such a mechanism is known to operate for the alkaline hydrolysis of many activated amides [3] and is represented by Scheme I. Equation 2 represents the rate

Scheme I

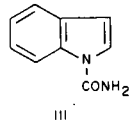


for the mechanistic scheme:

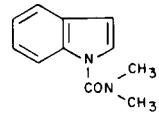
$$k_{obs} = \frac{k_1k_4[OH^-] + k_1k_3[OH^-]^2}{k_2 + k_4 + k_3[OH^-]} \qquad \text{Eq. 2}$$

Recently it was shown that the mechanism of the basic hydrolysis of *N*-acylpyrroles, *N*-acylindoles and *N*-acylcarbazoles [4,6] resembles that of activated amides rather that of simple amides. Furthermore the mechanism of hydrolysis of *N*-alkoxycarbonylpyrroles and -indoles parallels that of *p*-nitrophenylcarbamate [7].

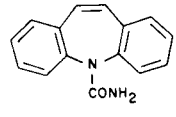
We wish now to report a study of the kinetics and mechanism of the basic hydrolysis of indole-1-carboxamide (III) and indole-1-(*N*,*N*-dimethyl)carboxamide (IV) at 60.0° and 0.3-2.4*N* hydroxide ion concentration and to compare the obtained data with those of carbamazepine [(5*H*-dibenz[*b*,*f*]azepine)-5-carboxamide] (V), a potent anticonvulsant drug.



III



IV



V

Results and Discussion.

Plot of $k_{obs}/[OH^-]$ *vs* [OH^-] is curved for carbamazepine showing that at low base concentration the hydrolysis is mainly second order in hydroxide ion while at high base concentration is first order in hydroxide ion. Analogous plots for III and IV are parallel to the abscissa showing that in the [OH^-] range concentration (0.3-2.4*N*) at which rates where measured the hydrolysis is essentially first order in [OH^-]. The k_1 rate constants, collected in Table 1, have been calculated according to the method of Kershner and Schowen [3] and from the average value of $k_{obs}/[OH^-]$ for III and IV. The results obtained from literature, for urea and *N*,*N*,*N'*,*N'*-tetramethylurea, have been elaborated by fitting the data according to Eq 2.

Table 1

Rate Constants for the Hydroxide-Catalyzed Hydrolysis of Ureas and Carboxamides in Water at 60.0° ± 0.2
(μ = 3.0, added sodium perchlorate)

Compound	$k_1(M^{-1}sec^{-1})$	$k_3/k_2(M^{-1})$
Urea (I)	2×10^{-6}	1
N,*N*,*N'*,*N'*-Tetramethylurea (II)	4.6×10^{-6}	0.35
Indole-1-carboxamide (III)	2.2×10^{-3}	
Indole-1-(*N*,*N*-dimethylcarboxamide) (IV)	2.2×10^{-3}	
Carbamazepine (V)	$7.5 = 10^{-7}$	1

From the data of Table 1 we can observe that the two ureas, I and II, were very stable and are hydrolyzed at similar rates under these conditions and that carbamazepine (V) is even more stable and is more slowly hydrolyzed probably because of steric hindrance of *peri*-hydrogens to the attack of hydroxide ion.

The rate constants of formation of the tetrahedral intermediate are increased by *N*-substitution with a heteroaromatic ring by a factor of 10^3. Similar enhancement has been observed previously in *N*-acylpyrroles in the respect of *N,N*-dimethylacetamide (10^4 value) [8] and in *N*-ethoxycarbonylpyrrole in the respect of *N,N*-dimethylethylcarbamate (10^4) [7]. The high reactivity of the *N*-acyl, *N*-alkoxycarbonyl and *N*-carbamoyl heteroaromatics is readily understandable because the carbon-nitrogen conjugation is considerably reduced as compared with simple amides, carbamates and ureas as shown by physical evidence (ir, barriers of rotation) [9]. As a consequence carbon atom is particularly suitable for the nucleophilic attack of hydroxyde ion and the enhanced electron delocaliztion in the heteroaromatic nucleus favours ejection of the leaving group.

The fact that the reaction is first order in hydroxide ion for III and IV is probably due to a delicate balance between factors affecting the various steps of the reaction as previously shown for *p*-nitrobenzoylpyrrole [8]. Finally the very low reactivity of carbamazepine is certainly due to steric hindrance of *peri*-hydrogens to the attack of hydroxide ion and the fact that 5*H*-dibenz[*b,f*]azepine has been found together with carbamazepine in human urine [10] suggests the existence of an enzyme pathway for its biotransformation.

EXPERIMENTAL

Materials.

All chemicals used were analytically pure grade and carbamazepine [11] was used without further purification. Indole-1-(*N,N*-dimethyl)carboxamide (III) was prepared following the method previously described [12].

Synthesis of Indole-1-(carboxamide) (III).

To a well stirred solution of indole-1-carboxylic acid (4.7 g, 29 mmoles) [3] in chloroform a solution of phosphorus pentachloride (7 g) in chloroform was added dropwise at 0°. After one hour the mixture was evaporated *in vacuo* at 30-40° and the residue was extracted with diethyl ether and filtered.

The yellow solution was cooled in and ice-bath and stirred, then anhydrous gaseous ammonia was bubbled through the reaction mixture. The ethereal solution was washed with water, dried and evaporated. The residual crude indole-1-carboxamide was recrystallized from methanol and then from water, yield 50%, mp 174-176° (lit 174-175°) [14]; ir (mineral oil): 3350, 3190, 1735 cm^{-1}; nmr (deuterioacetone): δ 6.7 (d, 1H, indole-3-proton), 6.95 (m, 2H, amino group), 7.1-7.75 (m, 3H, aromatic protons), 7.85 (d, 1H, indole-2-proton), 8.3 (m, 1H, indole-7-proton).

Kinetic Studies.

A solution of III and IV in acetonitrile ($1 \times 10^{-2}M$) was used as a stock solution for kinetic measurements. A stoppered cuvette containing 2.5 or 3 ml of an aqueous sodium hydroxide solution was thermostated at 60.0° ± 0.2 within the cell compartment. The reaction was initiated by addition of 10-20 μl of stock solution. Final concentration of substances were from 10^{-4} to $10^{-5}M$, the ionic strength (μ = 3.0) was maintained constant by adding sodium perchlorate. In the case of V it was dissolved in the appropriate basic solution in order to have a 10^{-4}-$10^{-5}M$ concentration. This solution was transferred into ampullae of neutral glass, sealed and thermostated at 60.0° ± 0.2 into a water bath. The first sample was withdrawn as soon as the thermal equilibrium was reached and subsequent samples were taken at appropriate time intervals to measure the absorbance value.

Hydrolyses were followed spectrophotometrically and monitoring wavelengths, expressed in nm, were the following III (235), IV (240) and V (250).

Pseudo-first-order rate constants were calculated form absorbance *vs* time data using least square treatment by means of desk computer.

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