Solvolysis of *O*-acyl-10-hydroxy-10,11-dihydro-indeno[1,2-*c*]isoquinolin-5,11-diones

[a]T. KUČEROVÁ, [a]J. MOLLIN, and [b]J. MICHALSKÝ

[a]*Department of Inorganic and Physical Chemistry, Faculty of Natural Sciences, Palacký University, 771 46 Olomouc*

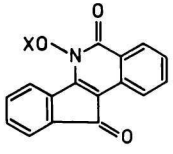
[b]*Pharmacy and Biochemistry Research Institute, 130 60 Prague*

Received 22 June 1977

The rate of the solvolysis of *O*-acyl-10-hydroxy-10,11-dihydroindeno[1,2-*c*]isoquinolin-5,11-diones and of the corresponding *p*-nitrophenyl esters under neutral conditions has been determined. It follows from the comparison of the rates as well as from the p*K* values of the corresponding acids and the activation entropies found for the process of the solvolysis that the reaction, affected also by steric effects, is governed by the S_N2 mechanism.

Скорость нейтрального сольволиза *O*-ацилпроизводных 10-гидрокси-10,11-дигидро-индено[1,2-*c*]изохинолин-5,11-диона была сравнена со скоростью нейтрального сольволиза соответствующих *п*-нитрофенильных сложных эфиров. На этом основании было найдено, по значениям p*K* соответствующих кислот и найденым энтропиям активации реакции сольволиза, что реакция сольволиза в изучаемой группе соединений протекает по механизму S_N2 при явном влиянии стерических эффектов.

Racemization of optically active substances is an unwanted side reaction in the chemistry of optically active peptides. This process can be minimized by using sufficiently reactive starting materials so that the syntheses can be carried out under mild conditions. The outlined trend resulted in the introduction into the modern chemistry of peptides of reactive esters based on hydroxylamine [1—3]. Synthesis of some *O*-acyl-10-hydroxy-10,11-dihydroindeno[1,2-*c*]isoquinolin-5,11-diones has been recently described [4].



X = H, acyl

The present work deals with the reactivity of the above-mentioned class of substances under the conditions of simple nucleophilic addition reaction — neutral solvolysis. The results are compared with the rates of the neutral solvolysis of some *p*-nitrophenyl esters which are also used in the chemistry of peptides [1].

Experimental

The synthesis of the derivatives of 10,11-dihydroindeno[1,2-*c*]isoquinolin-5,11-dione [10-hydroxy- (*I*), 10-acetoxy- (*II*), 10-propionyloxy- (*III*), 10-senecioyloxy- (*IV*), 10-benzoyloxy- (*V*), 10-(α-phenylbutyryloxy)- (*VI*), 10-(*N*-benzyloxycarbonylglycyl-L-prolyloxy- (*VII*)] has been described elsewhere [4]. Senecic (*XI*) [5] and α-phenylbutyric (*XII*) [6] acids and *N*-benzyloxycarbonylglycyl-L-proline (*XIII*) [7], as well as *p*-nitrophenyl esters of acetic (*XIV*) [8], benzoic (*XV*) [9], propionic (*XVI*) [10], and α-phenylbutyric (*XVII*) [11] acids were prepared according to the literature cited. The prepared substances gave correct elemental analyses and their melting points agreed with the literature data. Acetic (*VIII*), propionic (*IX*), and benzoic (*X*) acids as well as the used *p*-nitrophenol (*XVIII*) were commercial products of reagent grade purity (Lachema, Brno).

Working procedures

The p*K* values for the acids *VIII*—*XIII* and *XVIII* were determined by titration in the following manner. The solutions (1.00×10^{-2} mol dm^{-3}) were prepared in 50% (w/w) ethanol. They were stabilized by an addition of sodium perchlorate (reagent grade; Lachema, Brno) and had an ionic strength $I = 0.1$ mol dm^{-3}. The solutions were titrated with 1.0×10^{-1} M sodium hydroxide (reagent grade; Lachema, Brno), prepared in the same solvent. The pH was measured with a glass and a silver chloride electrode, as described [12]. Because of the poor solubility of *I* its p*K* was determined spectrophotometrically at 518 nm at a concentration of 2.0×10^{-4} M. In this case a mixture of citric acid (0.100 M, reagent grade; Lachema, Brno), sodium citrate (0.100 M, reagent grade; Lachema, Brno), triethanolamine (5.00×10^{-2} M, reagent grade; Lachema, Brno), perchloric acid ($5.0 \times$ $\times 10^{-1}$ M, reagent grade; Jenapharm), glycine (5.00×10^{-2} M, reagent grade; Lachema, Brno), and sodium hydroxide (1.50×10^{-1} M in 50% (w/w) ethanol) was used as a buffer. For the calculations of p*K* the activity coefficients of ions were assumed to be equal to unity.

The kinetic measurements were performed discontinuously. Ethanolic solutions (50% (w/w) ethanol) of *II*—*VII* (2.50×10^{-4} M) and *XIV*—*XVII* (3×10^{-5} M) were prepared in the above-mentioned buffers. Sealed ampules containing the respective solutions were heated (±0.1°C) by means of an ultrathermostat and, periodically, their content was analyzed (after cooling) with the aid of a Spectromom 202 (MOM, Budapest) instrument using 1 cm quartz cells. The hydrolysis of *II*—*VII* was monitored by means of the reaction of *I*, formed in the course of the hydrolysis with Fe^{3+} ions to give a hydroxamate complex. A sample of the analyzed solution (5 ml) was mixed with 1 ml of 0.100 M ferric ammonium sulfate (reagent grade; Lachema, Brno) in aqueous 1.0 M sulfuric acid. The absorbance of the discolouration was measured at 460—510 nm. The hydrolysis of *XIV*—*XVII* was

monitored by measuring the absorbance in the u.v. region. The respective wavelengths are given in Table 2. The concentration changes *vs.* time for the compounds under investigation agreed formally to isolated first-order reaction at least up to 75% conversion. The rate constants were calculated by the least-square method according to the equation

$$\ln [(A_0 - A_\infty)/(A - A_\infty)] = kt \qquad (1)$$

where A_0 is the starting absorbance, A is the absorbance at the time t, and A_∞ is the absorbance at a sufficiently long period at which time A altered only within the experimental error. The rate constants, calculated in this manner, showed an error of less than 5%. The dependence of the rate constants *vs.* pH for *II—VII* was determined at 60°C and that for *XIV—XVII* at 90°C. For the calculation of the activation parameters the rate constants obtained at 60, 70, 80, and 90°C were used.

Results and discussion

The pK values found for the acids in 50% (w/w) ethanol are given in Table 1. The rate constants of the hydrolysis of esters depend upon the activity of H^+ and OH^- ions according to the general equation

$$k = k_{H^+} + k_{neutr} + k_{OH^-} \qquad (2)$$

For the hydrolysis of *O*-acyl hydroxamic acids a similar dependence of rate constants *vs.* pH has been found [13]. The aminolysis of active esters to give peptides, often carried out in aprotic solvents, resembles most closely neutral

Table 1

pK Values found for the acids in 50% (w/w) ethanol at 20°C ($I = 0.1$ mol dm^{-3})

Acid	pK	Acid	pK
I	6.00 ± 0.05	*XI*	6.41 ± 0.03
VIII	5.31 ± 0.03	*XII*	5.67 ± 0.03
IX	5.75 ± 0.03	*XIII*	4.47 ± 0.02
X	5.10 ± 0.03	*XVIII*	7.51 ± 0.02

hydrolysis. Therefore, our attention was focused mainly to such conditions under which the rate constant of the solvolysis does not depend upon the activity of H^+ ions. The results obtained are summarized in Table 2. It is obvious that under weakly acidic conditions the rate constant does not depend upon pH, under alkaline conditions the reaction is speeded up. The common concept of the mechanism of base-catalyzed solvolysis [14] assumes the tangency of the dependence of the logarithm of the rate constant *vs.* pH to be equal to unity. From the

Table 2

Rate constants of neutral and base-catalyzed solvolyses for *II*—*VII* (60°C) and *XIV*—*XVII* (90°C) in 50% (w/w) ethanol

Compound λ, nm	pH	$k \cdot 10^5$, s^{-1}	Compound λ, nm	pH	$k \cdot 10^5$, s^{-1}
II			*VII*		
460	2.90	12.3	470	3.25	2.47
	4.02	12.3		4.30	1.84
	5.02	12.4		5.14	2.22
	6.17	16.5			
	7.00	34.2	*XIV*		
	8.10	73.8	265	3.66	2.81
	8.80	131.9		4.50	3.28
	10.60	665.0		5.18	4.55
	10.98	701.0		6.08	15.1
	11.30	1280.0	*XV*		
III			270	5.40	0.68
490	2.90	8.45		6.08	0.661
	4.25	9.37		7.20	2.40
	5.02	9.98	*XVI*		
			262	3.70	1.72
IV				4.50	1.80
490	4.10	1.20		5.40	1.92
	5.02	1.22		6.08	11.05
	6.17	1.13			
			XVII		
V			270	3.88	0.73
460	3.25	1.00		4.31	0.719
	4.30	1.02		5.06	0.701
	5.14	1.07		5.67	2.20
VI					
510	3.25	0.701			
	4.30	0.721			
	5.14	0.742			

data found for *II* a value of 0.4 was found for this tangency. Owing to a very poor water solubility of *II* the discrepancy between the found and the expected value could not be clarified.

It is known that the rate of aminolysis [15] and solvolysis [16] of active esters depends, with a given acyl, upon pK of the group being cleaved and upon the steric factors. The model substance studied herein differs somewhat in principle from those studied previously: the group being split is the same and the acyl group is different in each particular case. The comparison of the pK and rate constants at pH 5.02 and 5.14 (Table 2) shows that the acidity of the acid from which the acyl

group is derived is less important for the rate of the neutral solvolysis than its steric effect. Slow reactions, compared to *II* and *III*, were observed for compounds *V* and *VI* bearing bulky acyl groups, although the pK of the corresponding acids differ but little. On the other hand, the rate constants of the neutral solvolysis of *V* and *VI* are about the same as those of *IV*, although *XI* is a weaker acid than are *X* and *XII*. To clarify the effects which govern the neutral solvolysis of *II*—*VII* the rate constants of these reactions were compared with those of the neutral solvolysis of *O*-acyl *p*-nitrophenols *XIV*—*XVII*. These models were chosen firstly because *p*-nitrophenyl esters are used in peptide chemistry anyway, and secondly because the neutral solvolysis of this class of substances is influenced but little by inductive and mesomeric effects [17]. The found values are given in Table 2. It becomes obvious when the rate constants of the neutral solvolysis found for the two groups of substances are compared, taking into account also the pK values (Table 1), that the inductive and mesomeric effects are less important for both groups of compounds than are the steric effects. These manifest themselves more strongly with the acyl derivatives of *I* than with the phenyl esters.

To clarify the mechanism of the neutral solvolysis the activation parameters for the compounds under investigation have also been measured (Table 3). In agreement with the literature [18, 19] the found activation entropy values suggest for the rate-determining step a concept of a slow nucleophilic addition catalyzed by another molecule of the solvent.

Table 3

Activation parameters for the neutral solvolyses at 70°C in 50% (w/w) ethanol

Compound	*II*	*III*	*IV*	*V*	*VI*	*VII*	*XIV*	*XV*	*XVI*	*XVII*
ΔH^{+} kJ mol^{-1}	58.8	46.3	52.7	42.2	48.5	58.7	40.6	35.7	40.9	39.0
ΔS^{+} J mol^{-1} K^{-1}	144	185	187	215	198	161	222	249	190	240
pH	4.05	4.25	4.25	4.30	4.30	4.30	4.50	5.71	5.40	5.06

Summarizing the obtained results it can be concluded, that in the rate-determining step the neutral solvolysis of *O*-acyl derivatives of *I* is governed by a mechanism accepted for a bimolecular nucleophilic addition. The reaction is affected also by steric effects. Based on the observation during syntheses [4] it seems likely that the same conclusions hold also for the aminolysis of this class of substances. Therefore, the more favourable will be the steric conditions of the reaction, the more advantageous will be the use of the acyl derivatives of *I* in the peptide chemistry.

References

1. *Methoden der organischen Chemie* (Houben—Weyl). Vol. *15/2*, p. 130. Thieme, Stuttgart, 1974.
2. König, W. and Geier, R., *Chem. Ber.* ***103,*** 788 (1970).
3. Pless, J., *Peptides. Proceedings of the 5th European Peptide Symposium, Oxford, 1962.* Pergamon Press, Oxford, 1963.
4. Hebelka, M., *Thesis.* Palacký University, Olomouc, 1977.
5. Wenig, M., *Justus Liebigs Ann. Chem.* ***280,*** 255 (1894).
6. Neure, K., *Justus Liebigs Ann. Chem.* ***250,*** 140 (1889).
7. Agarwal, K. Z., Kenner, G. W., and Sleppard, R. C., *J. Chem. Soc.* ***1968,*** 1384.
8. Kaufmann, A., *Ber. Deut. Chem. Ges.* ***42,*** 3480 (1909).
9. Neumann, G., *Ber. Deut. Chem. Ges.* ***19,*** 2018 (1886).
10. Boit, H. G., *Beilsteins Handbuch der organischen Chemie,* 4th Ed., Vol. *6,* p. 826. Springer-Verlag, Berlin, 1965.
11. Dupaix, A., Bechet, J., and Roucous, C., *Biochemistry* ***1973,*** 2559.
12. Mollin, J., Kašpárek, F., and Lasovský, J., *Chem. Zvesti* ***29,*** 39 (1975).
13. Ashfaq, A., Pytela, O., Socha, J., Večeřa, M., *Collect. Czech. Chem. Commun.* ***41,*** 3308 (1976).
14. Ingold, C. K., *Structure and Mechanism in Organic Chemistry* (Russian translation), p. 936. Mir, Moscow, 1973.
15. Pless, J. and Boissonnas, R. A., *Helv. Chim. Acta* ***46,*** 1609 (1963).
16. Gold, V., Oakenfull, B. G., and Riley, T., *J. Chem. Soc.* ***B1968,*** 515.
17. Mollin, J. and Baisa, A. A., *Collect. Czech. Chem. Commun.*, in press.
18. Engbersen, J. F. J. and Engberts, J. B. F. N., *J. Amer. Chem. Soc.* ***96,*** 1231 (1974).
19. Fife, T. H. and De, N. C., *J. Amer. Chem. Soc.* ***96,*** 6158 (1974).

Translated by P. Kováč