Tetrahedron Vol. 38, No. 10, pp. 1517 to 1521, 1982
Printed in Great Britain.

0040-4020/82/101517-05$03.00/0

MECHANISMS FOR THE SOLVOLYTIC DECOMPOSITIONS OF NUCLEOSIDE ANALOGUES—VIII

ACIDIC HYDROLYSIS OF 5-SUBSTITUTED 1-(ALKOXYETHYL)CYTOSINES AND CYTIDINES

HARRI LÖNNBERG
Department of Chemistry and Biochemistry, University of Turku, SF-20500 Turku, Finland

(*Received in U.K. 29 October* 1981)

Abstract—Several 5-substituted 1-(1-alkoxyethyl)cytosines have been prepared and the rate constants for their hydrolysis determined at various concentrations of oxonium ion. The acidity constants for the monoprotonated substrates and the rate constants for their decomposition have been calculated from the pH-rate profiles obtained. The effects that varying the polar nature of the 1-alkoxyethyl group exerts on the heterolysis of the monoprotonated substrates are interpreted to indicate that the acidic hydrolysis of 1-(1-alkoxyethyl)cytosines proceeds by rate-limiting departure of the protonated base moiety with formation of an oxocarbenium ion intermediate. The same mechanism is extended to the hydrolysis of cytidines by comparing the influences that the 5-substituents have on the heterolysis of protonated 5-substituted 1-(1-ethocyethyl)cytosines and correspondingly substituted cytidines.

Several lines of evidence[1-9] suggest that the acidic hydrolysis of purine nucleosides involves a rapid initial protonation of the substrate, giving a mono- and dication, and a subsequent rate-limiting formation of a cyclic glycosyl oxocarbenium ion. Shapiro *et al.*[10,11] have proposed an analogous mechanism for the hydrolysis of 2'-deoxypyrimidine nucleosides. However, later on thymidine and 2'-deoxyuridine have been shown to undergo anomerization to pyranoid and α-furanoid derivatives under conditions where the hydrolysis occur.[12] Accordingly, the hydrolysis might, at least partially, proceed by protonation of the ring-oxygen of the glycone moiety followed by cleavage of the *endo*cyclic C–O-bond to give a Schiff base intermediate.[12] The aim of the present study is to distinguish between these two alternative pathways in the hydrolysis of cytidine. For this reason, the hydrolysis of simple acyclic analogues of cytidine, 1-(1-alkoxyethyl)cytosines, has first been shown to occur *via* oxocarbenium ion intermediates. By comparing the structural effects in the hydrolysis of 5-substituted 1-(1-ethoxyethyl)cytosines and correspondingly substituted cytidines, the same mechanism is then extended to the decomposition of the latter compounds.

RESULTS AND DISCUSSION

Figure 1 shows the dependence of the first-order rate constants for the hydrolysis of 1-(1-alkoxyethyl)cytosines on the oxonium ion concentration of the reaction solution at 363.2K. With each compound the hydrolysis rate is almost completely independent of the acidity in the range of $10^{-3}\,\text{mol dm}^{-3} < [H^+] < 0.1\,\text{mol dm}^{-3}$. At lower acidities the observed rate constant, k(obs), becomes linearly related to $[H^+]$. In concentrated acid solutions the hydrolysis rate increases considerably again. It should be noted that the rate-accelerations in the latter case are far greater than those expected to be produced by the changes in the ionic strength on going from $1^{-3}\,\text{mol dm}^{-3}$ acid solution. For comparison, the rate constant for the hydrolysis of 1-(1-ethoxyethyl)cytosine, measured in $0.1\,\text{mol dm}^{-3}$ perchloric acid, increases only by 25% as the ionic strength is increased to $3\,\text{mol dm}^{-3}$ with sodium perchlorate. Similar pH-rate profiles have been reported for the hydrolysis of 5-substituted 2'-deoxycytidines.[11]

The two alternative hydrolysis mechanisms proposed for pyrimidine nucleosides[10-12] are depicted for their acyclic analogues, 1-(1-alkoxyethyl)cytosines, in Scheme 1. The pH-rate profiles indicated above can well be accounted for by route A. On the basis of literature data[13] the acidity constants of the mono- and diprotonated substrates are expected to fall in the ranges of $10^{-5}\,\text{mol dm}^{-3} < K_1 < 10^{-3}\,\text{mol dm}^{-3}$ and $K_2 > 1\,\text{mol dm}^{-3}$. Accordingly, at low acidities the concentration of the dication, SH_2^{2+}, is negligible, and the reaction *via* the monocation, SH^+, most probably prevails. Under such conditions, k(obs) increases with the increasing oxonium ion concentration, owing to the increment in the concentration of SH^+, and levels off to a constant value of k_1 when the substrate becomes completely protonated. At high acidities the reaction *via* the

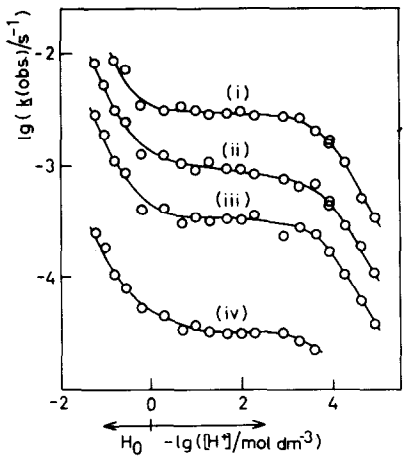
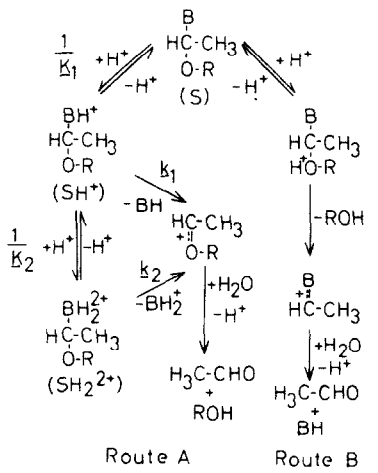


Fig. 1. Dependence of the first-order rate constants for the hydrolysis of 1-(1-alkoxyethyl)cytosines on the oxonium ion concentration at 363.2K. For the composition of the reaction solutions see the experimental. Notation (i) isopropoxy, (ii) ethoxy, (iii) methoxy, and (iv) 2-chloroethoxy derivative.



Scheme 1.

dication, SH_2^{2+}, is significant, and the hydrolysis rate begins to increase again. The latter rate-enhancement is difficult to explain by route B. The hydrolyses proceeding *via* Schiff bases are generally slowed down at high oxonium ion concentrations, since the decomposition of the hydrated Schiff base, needing base catalysis, becomes rate-limiting under highly acidic conditions.[14]

The rate-law for route A may be expressed by eqn (1). Evidently the

$$\frac{d[P]}{dt} = k_1[SH^+] + k_2[SH_2^{2+}] = \frac{\frac{[H^+]}{K_1}\left(k_1 + \frac{k_2}{K_2}[H^+]\right)}{1 + \frac{[H^+]}{K_1} + \frac{[H^+]^2}{K_1K_2}}[S(tot.)] \quad (1)$$

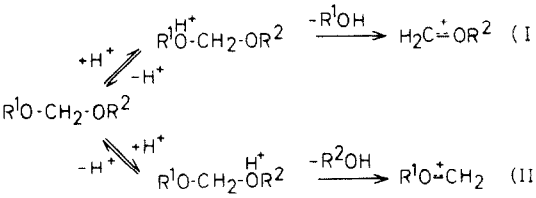
terms referring to the concentration of SH_2^{2+} and its decomposition can be neglected at low oxonium ion concentrations, i.e. at $[H^+] < 10^{-2}$ mol dm^{-3}. Consequently, eqn (2) well approximates the dependence of k(obs) on $[H^+]$ under such conditions. The latter equation can easily be transformed to eqn (3), which indicates that plotting of

$$k(obs) = \frac{k_1[H^+]}{K_1 + [H^+]} \quad (2)$$

$$k(obs) = k_1 - K_1\frac{k(obs)}{[H^+]} \quad (3)$$

k(obs) against the apparent second-order rate constant, k(obs)/$[H^+]$, yields a straight line with the slope and intercept equal to $-K_1$ and k_1, respectively. The values obtained for k_1 and K_1 by this method are listed in Table 1. In principle, substitution of k_1 and K_1 in eqn (1) enables a similar treatment to obtain k_2 and K_2. However, the justification of this procedure is doubtful, since it is difficult to predict how k_2 and K_2 respond to changes of the ionic strength in concentrated acid solutions.

Conclusive evidence for the suggestion that route A is utilized in the hydrolysis of 1-(1-alkoxyethyl)cytosines comes from the effects that varying the polar nature of the alkoxy group exerts on the rate constants, k_1, for the heterolysis of the protonated substrates. As seen from Table 1, k_1 decreases markedly with the increasing electronegativity of the alkoxy group. This is expected on the basis of mechanism A, since electron withdrawal by the alkoxy group lowers the electron density at Cl′ of the Et group, and thus destabilizes the oxocarbenium ion developing in the rate-limiting stage. The observed structural effects can well be compared to the influences that the nondeparting alkoxy group, OR^2, has on the rate of reaction I (Scheme 2) of acyclic acetals. Salomaa[15] has shown the relative rate constants for this partial reaction to be 22.1, 4.48, 1, and 0.0480, when R^2 is i-Pr, Et, Me, and 2-chloroethyl, respectively. These values predominantly reflect the effect of R^2 on the stability of the oxocarbenium ion, since the influence on the protonation step is presumably small, owing to the long distance between R^2 and the site of protonation. Figure 2 clearly indicates that the structural effects are in the heterolysis of protonated 1-(1-alkoxyethyl)cytosines quite similar to those in partial reaction I of acetals. This finding strongly suggests that the reactions occur *via* closely related intermediates. In other words, the cytosine derivatives are most probably hydrolyzed *via* oxocarbenium ions derived from the 1-alkoxyethyl group, as described by route A. The slightly greater susceptibility observed in the acetal hydrolysis may possibly be attributed to the influences of R^2 on the pre-equilibrium protonation.



Scheme 2.

Table 1. Acidity constants, K_1, for monoprotonated 1-(1-alkoxyethyl)cytosines, and the first-order rate constants, k_1, for their hydrolysis at 363.2K[a]

Alkoxy group	$K_1/10^{-5}$ mol dm^{-3}	$k_1/10^{-3}$ s^{-1}
Isopropoxy	9 ± 1	3.02 ± 0.09
Ethoxy	8 ± 1	0.850 ± 0.040
Methoxy	9 ± 1	0.324 ± 0.018
2-Chloroethoxy	9 ± 1	0.0329 ± 0.0020

[a]The ionic strength adjusted to 1 mol dm^{-3} with sodium perchlorate.

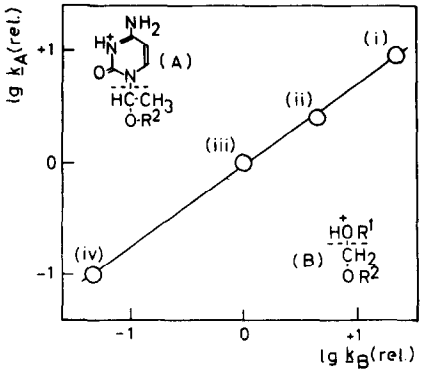


Fig. 2. Comparison of the structural effects in the decomposition of protonated 1-(1-alkoxyethyl)cytosines with those in the partial reaction I (see Scheme 2) of acetals of formaldehyde.[15] Notation: (i) isopropoxy, (ii) ethoxy, (iii) methoxy, and (iv) 2-chloroethoxy derivatives.

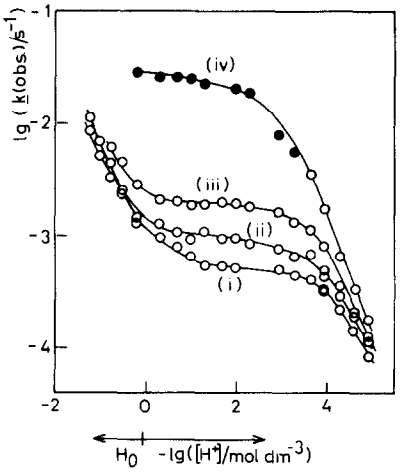


Fig. 3. Dependence of the first-order rate constants for the hydrolysis of 5-substituted 1-(1-ethoxyethyl)cytosines on the oxonium ion concentration at 363.2K. The filled circles are obtained by extrapolation *via* the Arrhenius equation from rate constants measured at lower temperatures. For the composition of the reaction solutions see the experimental. Notation: (i) methyl, (ii) unsubstituted, (iii) hydroxymethyl, and (iv) bromo derivative.

The first-order rate constants for the hydrolysis of some 5-substituted 1-(1-ethoxyethyl)cytosines at 363.2K are presented as a function of the oxonium ion concentration in Fig. 3. The pH-rate profiles are similar to those observed for 1-(1-alkoxyethyl)cytosines, suggesting that introduction of the 5-substituents in the substrate does

Table 2. Acidity constants, K_1, for monoprotonated 5-substituted 1-(1-alkoxyethyl)cytosines, and the first-order rate constants, k_1, for their hydrolysis at 363.2K[a]

5-Substituent	$\underline{K}_1/10^{-5}$ mol dm^{-3}	$\underline{k}_1/10^{-3}$ s^{-1}
Methyl	6 ± 1	0.510 ± 0.011
Hydrogen	8 ± 1[b]	0.850 ± 0.040[b]
Hydroxymethyl	17 ± 2	1.88 ± 0.09
Bromo	140 ± 20	22.6 ± 2.0

[a]The ionic strength adjusted to 1 mol dm^{-3} with sodium perchlorate.[b] From Table 1.

Table 3. First-order rate constants for the hydrolysis of 5-substituted cytidines in aqueous hydrogen chloride at 393.2K[a]

5-Substituent	[H^+]/mol dm^{-3}	$\underline{k}$(obs.)/10^{-5} s^{-1}
Methyl	0.20	1.6 ± 0.1
	0.050	1.7 ± 0.1
	0.010	1.7 ± 0.1
Hydrogen	0.20	2.5 ± 0.1
	0.050	2.6 ± 0.1
	0.010	2.2 ± 0.1
Hydroxymethyl	0.20	6.2 ± 0.2
	0.050	6.5 ± 0.3
	0.010	6.0 ± 0.3
Bromo	0.20	86 ± 3
	0.050	89 ± 4
	0.010	62 ± 3

[a]The ionic strength adjusted to 1 mol dm^{-3} with sodium chloride.

not change the hydrolysis mechanism. Application of eqn (3) to the kinetic data yields the partial rate anid equilibrium constants, k_1 and K_1, given in Table 2. The kinetically determined values of K_1 agree with those obtained potentiometrically for the same substances (Table 5) at 298.2K. The values of k_1 increase considerably with the increasing electron-attracting character of the 5-substituent, as expected on the basis of route A. Electronegative substituents in the departing group lower the electron density at Nl, and hence facilitate the rate-limiting rupture of the C–N-bond. If the same mechanism operates in the hydrolysis of cytidines, the effect of the 5-substituents on the heterolysis of the protonated nucleosides should also be the same. Table 3 records the first-order rate constants for the hydrolysis of 5-substituted cytidines at oxonium ion concentration ranging from 0.01 mol dm^{-3} to 0.2 mol dm^{-3}, i.e. in the range where the hydrolysis rates of the corresponsingly substituted 1-(1-ethoxyethyl)cytosines are independent of the acidity of the reaction solution. As seen from Table 3, this is also the case with 5-substituted cytidines. Accordingly, the observed rate constants are equal to the rate constants, k_1, for the heterolysis of the protonated species. In Fig. 4 the values of k_1 for 5-substituted cytidines are compared with those for the corresponding 1-(1-ethoxyethyl)cytosines. It is clearly seen that the structural effects are almost identical with both series of compounds. The latter finding strongly suggests that the hydrolysis of cytidines proceeds analogous to the hydrolysis of 1-(1-alkoxyethyl)cytosines, i.e. by route A in Scheme 1.

Mild additional support for the preceding conclusion comes from the observation that 5-bromocytidine is not markedly anomerized under conditions where the hydrolysis occurs. After one half-time in 0.1 mol dm^{-3} deuterium chloride the substrate still exhibited only one

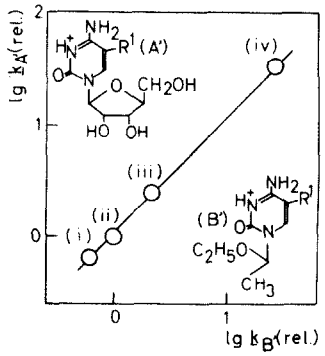


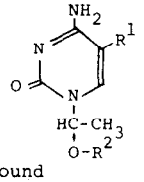
Fig. 4. Comparison of the structural effects in the decompositions of protonated 5-substituted cytidines and 1-(1-ethoxyethyl)cytosines. Notation: (i) methyl, (ii) unsubstituted, (iii) hydroxymethyl, and (iv) bromo derivatives.

^{1}H NMR signal, *viz.* Hl′ of the substrate at 5.82 ppm from DSS, in the anomeric proton region. The anomeric protons of nucleosides have been shown[16] to resonate at a higher field when the adjacent proton is *trans*, as in cytidines, than when *cis*. Accordingly, the anomeric proton signal of the α-furanoid anomer of the substrate would be expected to occur at 5.8–6.3 ppm from DSS. In this range no signal appeared during the hydrolysis.

EXPERIMENTAL

Materials. 5-Substituted 1-(1-alkoxyethyl)cytosines were prepared by treating the appropriate 5-substituted cytosines in DMF soln with equal amounts of alkyl 1-chloroethyl ethers synthesized as described earlier.[17,18] The temp of the mixture was kept between 60 and 80°. Et_3N was added to neutralize the HCl liberated in the condensation reactions. Its hydrochloride was filtrated from the cooled soln and the solvent was removed under reduced pressure. The products were crystallized as their picrates from MeOH. Before kinetic measurements 5-substituted 1-(1-

Table 4. ^{1}H and ^{13}C NMR chemical shifts[a] for 5-substituted 1-(1-alkoxyethyl)cytosines



I: R^1 = H, R^2 = $CH(CH_3)_2$
II: R^1 = H, R^2 = CH_2CH_3
III: R^1 = H, R^2 = CH_3
IV: R^1 = H, R^2 = CH_2CH_2Cl
V: R^1 = CH_3, R^2 = CH_2CH_3
VI: R^1 = CH_2OH, R^2 = CH_2CH_3
VII: R^1 = Br, R^2 = CH_2CH_3

Compound		δ(2)	δ(4)	δ(5)	δ(6)	δ(1′)	δ(2′)	δ(R^1)	δ(R^2)		
I	^{1}H NMR:	-	-	d6.01	d7.66	q5.81	d1.29	-	h3.56	t0.98	
	^{13}C NMR:	157.4	166.4	99.0	144.8	83.5	23.4	-	74.1	24.4	23.1
II	^{1}H NMR:	-	-	d6.06	d7.66	q5.79	d1.39	-	q3.45	t1.09	
	^{13}C NMR:	160.6	168.6	99.4	143.6	85.4	23.0	-	67,2	16.6	
III	^{1}H NMR:	-	-	d6.09	d7.64	q5.67	d1.39	-	s3.21		
	^{13}C NMR:	157.7	166.5	99.2	144.5	87.6	22.7	-	58.7		
IV	^{1}H NMR:	-	-	d6.01	d7.68	q5.76	d1.33	-	m3.56		
	^{13}C NMR:	156.1	165.4	99.0	145.2	86.1	22.7	-	45.6	71.8	
V	^{1}H NMR:	-	-	-	s7.42	q5.80	d1.39	s1.92	q3.43	t1.10	
	^{13}C NMR:	160.6	168.6	108.0	140.6	85.3	23.1	15.0	67.3	16.6	
VI	^{1}H NMR:	-	-	-	s7.69	q5.85	d1.41	s4.44	q3.46	t1.10	
	^{13}C NMR:	160.4	167.5	110.1	142.3	85.5	23.1	60.3	67.4	16.6	
VII	^{1}H NMR:	-	-	-	s7.90	q5.78	d1.40	-	q3.47	t1.10	
	^{13}C NMR:	159.6	165.5	92.5	144.2	86.3	23.2	-	67.6	16.6	

[a]In D_2O. Taken as ppm from DSS.

Table 5. Wavelengths of UV absorption maxima and minima for 5-substituted 1-(1-alkoxyethyl)cytosines, acidity constants for their conjugate acids, and m.ps for their picrates

R^1 [a]	R^2 [a]	λ(max)/nm[b]	λ(min)/nm[b]	lg(K_a/mol dm^{-3})[c]	m.p./°C
H	$CH(CH_3)_2$	270	250	- 4.3	262-5 d
H	CH_2CH_3	271	251	- 4.3	242-5 d
H	CH_3	270	251	- 4.3	242-5 d
H	CH_2CH_2Cl	272	251	- 4.2	295-9 d
CH_3	CH_2CH_3	278	256	- 4.4	300-5 d
CH_2OH	CH_2CH_3	275	254	- 3.8	232-6 d
Br	CH_2CH_3	288	263	- 2.8	241-4 d

[a]See the structure in Table 4. [b]At pH 7. [c]I = 0.1 mol dm^{-3}, T = 25°.

alkoxyethyl)cytosines were regenerated from their picrates by successive treatments of the aqueous pictate solns with a strong anion exchange resin (Dowex 1 × 8, mesh 20–50) loaded with OH ions. The products crystallized spontaneously after evaporation to dryness. Table 4 records the ^{1}H and ^{13}C NMR data for the compounds prepared. The chemical shifts for the C atoms of the base moieties closely resemble those observed for other N1 derivatives of 5-substituted cytosines.[19] The wavelengths of the UV absorption maxima are listed in Table 5 together with the potentiometrically (Metrohm EA 121 combined electrode) determined acidity constants for the protonated substrates and the m.ps of the picrates. The magnitude of the acidity constants clearly indicates that the 1-alkoxyethyl substituents are attached to N1 of the 5-substituted cytosines. For N3 derivatives pK_a values would be about 3 units greater.[20] Furthermore, the UV absorption maxima would be expected to occur at about 20 nm higher wavelengths.[20]

5-Hydroxymethyl-1-(β-D-ribofuranosyl)cytosine was prepared by a $SnCl_4$-catalyzed silyl Hilbert–Johnson reaction. Silylation of 5-hydroxymethylcytosine was performed by heating the free base in hexamethyldisilazane in the presence of trimethylchlorosilane, as described by Vorbruggen *et al.*,[21] and the solvent was removed by two successive codistillations with xylene. The residue was fused with 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose (Fluka AG) in acetonitrile soln using $SnCl_4$ as catalyst. The product was isolated and deacetylated in ammoniacal MeOH as described earlier.[21] The hydrochloride of the compound exhibited the following ^{1}H and ^{13}C NMR chemical shifts (in D_2O, ppm from DSS), in consistence with those reported for cytidine and its derivatives.[19] ^{1}H NMR: δ(H5') m 3.7–4.0, δ(H2',3',4') m 4.1–4.4, δ(5–CH_2OH) s 4.63, δ(H1') s 5.96, δ(H6) s 8.26. ^{13}C NMR: δ(5 – CH_2OH) 59.4, δ(C5') 62.7, δ(C2') 71.4, δ(C3') 76.8, δ(C4'). 86.9, δ(C1') 93.0, δ(C5) 108.6, δ(C6) 145.6, δ(C2) 160.9, δ(C4) 173.3. No sign of the signals of the α-anomer was observed. The neutral compound showed UV absorption maximum at 275 nm and minimum at 254 nm. The log (K_a/mol dm^{-3}) value for the hydrochloride was 3.6 at the ionic strength of 0.1 mol dm^{-3} at 25°. TLC on Silica gel GF_{254} (Merck) with the mixture of MeOH and EtOAc (4:1) as eluent indicated only one spot at R_F = 0.56. The other nucleosides employed in the kinetic measurements were commercial products of Sigma Chemical Company, and they were used as received.

Kinetic measurements. These were performed as described earlier,[22] when the temp was 90°. At 120° a sealed tube modification of the same technique was applied. The progress of hydrolyses was followed at 250 nm. The initial substrate concentration was of the order of 2×10^{-4} mol dm^{-3}.

Hydrolyses of 5-substituted 1-(1-alkoxyethyl)cytosines were carried out in aqueous perchloric acid and formic and acetic acid buffers. The ionic strength was adjusted to 1 mol dm^{-3} with sodium perchlorate unless the perchloric concentration was greater than that. The oxonium ion concentrations of the buffer solns were estimated on the basis of the data in Refs. 23–25. The H_0 values at 363.2K were assumed to be equal to those at 298.2K.[26]

Hydrolyses of 5-substituted cytidines were carried out in HCL aq at the ionic strength of 1 mol dm^{-3} adjusted with NaCl.

Acknowledgments—The author wishes to thank Mr. Erkki Heikkinen, BA, for his skillful assistance in preparing the compounds employed in kinetic measurements. The financial aid from the Finnish Academy, Division of Sciences, and the Foundation of the University of Turku is gratefully acknowledged.

REFERENCES

[1]J. A. Zoltewicz, D. F. Clark, T. W. Sharpless and G. Grahe, *J. Am. Chem. Soc.* **92**, 1741 (1970).
[2]J. A. Zoltewicz and D. F. Clark, *J. Org. Chem.* **37**, 1193 (1972).
[3]R. P. Panzica, R. J. Rousseau, R. K. Robins and L. B. Townsend, *J. Am. Chem. Soc.* **94**, 4708 (1972).
[4]L. Hevesi, J. B. Wolfson-Davidson, J. B. Nagy, O. B. Nagy and A. Bruylants, *Ibid.* **94**, 4715 (1972).
[5]E. R. Garrett and P. J. Mehta, *Ibid.* **94**, 8532 (1972).
[6]F. Jordan and H. Niv, *Nucl. Acids Res.* **4**, 697 (1977).
[7]R. Romero, B. Stein, G. H. Bull and E. H. Cordes, *J. Am. Chem. Soc.* **100**, 7260 (1978).
[8]J. L. York, *J. Org. Chem.* **46**, 2171 (1981).
[9]H. Lönnberg and R. Käppi, *Acta Chem. Scand.* **A35**, 419 (1981).
[10]R. Shapiro and S. Kang, *Biochemistry* **8**, 1806 (1969).
[11]R. Shapiro and M. Danzig, *Ibid.* **11**, 23 (1972).
[12]J. Cadet and R. Teoule, *J. Am. Chem. Soc.* **96**, 6517 (1974).
[13]R. M. Izatt, J. J. Christensen and J. H. Rytting, *Chem. Rev.* **71**, 439 (1971).
[14]W. P. Jencks, *Progr. Phys. Org. Chem.* **2**, 63 (1964).
[15]P. Salomaa, *Ann. Acad. Sci. Fenn. Ser. A II* **103**, 1 (1961).
[16]V. V. Alenin and V. D. Domkin, *Zh. Obsch. Khim.* **48**, 2629 (1978) and refs therein.
[17]R. Rübencamp, *Liebigs Ann.* **225**, 267 (1884).
[18]M. F. Shostakovskii and F. P. Sidelkovskaya, *Izv. Akad. Nauk SSSR Otd. Khim. Nauk*, 892 (1959).
[19]S. N. Rosenthal and J. H. Fendler, *Adv. Phys. Org. Chem.* **13**, 279 (1976).
[20]A. R. Katritzky and A. J. Waring, *J. Chem. Soc.*, 3046 (1963).
[21]H. Vorbrüggen, K. Krolikiewicz and B. Bennua, *Chem. Ber.* **114**, 1124 (1981).
[22]H. Lönnberg and R. Käppi, *Tetrahedron* **36**, 913 (1980).
[23]H. S. Harned and B. B. Owen, *J. Am. Chem. Soc.* **52**, 5079 (1930).
[24]H. S. Harned and N. D. Embree, *Ibid.* **56**, 1042 (1934).
[25]H. S. Harned and R. W. Ehlers, *Ibid.* **55**, 652 (1933).
[26]M. A. Paul and F. A. Long, *Chem. Rev.* **57**, 1 (1957).