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Kinetics of Saponification of Some Cyclic Esters

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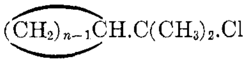
The alkaline hydrolysis of cycloalkane carbethoxylates (IV. R = C_2H_5, n = 3–6) has been measured at 0° and 25° in 41% aqueous ethanol, and the differences observed are discussed in terms of the steric and electronic effects of the rings.

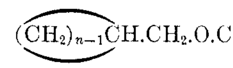
The effect of ring size on the rates of reactions taking place at a ring carbon atom has been well studied[2a] and the observed differences are consistent with the changes in ring strain occurring during the reaction.[2b] However very few data are available concerning the effects of ring size on a reaction center adjacent to the ring, where any differences in rate would be expected to be due to the steric and electronic effects of the ring and not directly to ring strain effects. Royals and Neal[3a] measured the rates of bimolecular displacement of cyclopentyl, cyclohexyl, and cycloheptyl methyl bromides (I, n = 5–7) with thiophenoxide ion finding a relative order of 1.00:1.46:2.95 at 35°, and Skinner and Florentine[3b] reported the rates of unimolecular solvolysis of cyclopentyl and cyclohexyl dimethylcarbinyl chlorides (II, n = 5,6) as having relative rates of 1.00:0.52 in 78% ethanol at 30°. Both of these reactions involve a carbon atom once removed from the ring. The rates of saponification of cycloalkanyl carbinyl acetates (III. n = 3–6) have been measured by Sarel, Tsai, and Newman,[4] who found values of k_2 ($\times$ 10^3 in l. mole^{-1} sec.$^{-1}$ in 70% dioxane-water at 20°) of 31, 23, 16, and 10 for the 3 to 6 ring compounds. The reaction, however, involves a displacement at the carbonyl-carbon atom which is three atoms removed from the ring. In the present work the rates of saponification of cycloalkane carbethoxylates (IV. R = C_2H_5, n = 3–6) have been measured in 41% ethanol-water at 25° and 0° (Table I). The rates showed an order of ring size of 4>>5>3~6 with relative differences of up to 11-fold, which is much greater than those found in the hydrolysis of the cyclic acetates (III). The reaction involves a displacement on the carbonyl-carbon atom which is only once removed from the ring, and an explanation for these relatively large differences must be sorted in the steric and electronic effects produced by the rings.


$(CH_2)_{n-1}CH.CH_2Br$

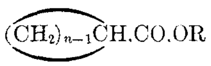
I


$(CH_2)_{n-1}CH.C(CH_3)_2.Cl$

II


$(CH_2)_{n-1}CH.CH_2.O.COCH_3$

III


$(CH_2)_{n-1}CH.CO.OR$

IV

The mechanism of bimolecular basic hydrolysis ($B_{AC}2$) of simple esters involves a slow rate determining attack of base on the carbonyl-carbon atom followed by a rapid elimination of alkoxide ion (ethoxide in this case) to form the acid anion. Electronic effects which decrease the charge on the carbonyl-carbon atom will accelerate the rate of nucleophilic attack of hydroxyl ion, whereas the steric hindrance of bulky neighboring substituents will decrease the ease of approach of a base. Cyclopropyl and cyclobutyl carboxylic acids have about the same acid strengths and are both stronger acids than cyclopentyl or cyclohexyl carboxylic acids (Table I).[5] This has been attributed[5a] to the increased s-character of the carbon-hydrogen bonds attached to the rings, resulting in a general electron-attracting ($-$I) effect. This effect is also reflected in the higher carbonyl stretching frequency of cyclopropyl carbethoxylate (Table II), and accounts for the high rate of saponification of the cyclobutyl ester (IV. R = C_2H_5, n = 4). However the much slower rate of hydrolysis of the cyclopropyl ester (IV. R = C_2H_5, n = 3) is not consistent with a purely electronic effect of the ring. In this case it is probable that the hydrogen atoms which are bunched together above and below the ring due to the increased s-character of the carbon-hydrogen bonds (the angle between sp^2-hybrids in 120°),[6] exert a steric hindrance to attack of base. The cyclobutane ring is, however, more open and the carbethoxy group will be less crowded.

There is little or no angle-strain present in a cyclopentane[7] or cyclohexane[2b] ring and their

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[2] (a) H. C. Brown, *J. Chem. Soc.*, 1248 (1956); (b) H. C. Brown, J. H. Brewster and H. Shechter, *J. Am. Chem. Soc.*, **76**, 467 (1954).

[3] (a) E. E. Royals and A. H. Neal, *J. Org. Chem.*, **21**, 1448 (1956); (b) G. S. Skinner and F. P. Florentine, *J. Am. Chem. Soc.*, **76**, 3200 (1954).

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[5] (a) J. D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.*, **73**, 5030 (1951); (b) M. Kilpatrick and J. G. Morse, *J. Am. Chem. Soc.*, **75**, 1854 (1953).

[6] The H—C—H angle in cyclopropane is 118–120°. O. Bastiansen and O. Hassel, *Tidsskr. Kjemi, Bergvesen Met.*, **6**, 71 (1946); P. W. Allen and L. E. Sutton, *Acta Cryst.*, **3**, 46 (1950).

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TABLE I

RATES OF SAPONIFICATION OF ESTERS[a]

Ester	pK_a Acid[a]	$k_2 \times 10^4$ L. Mole^{-1} Sec.$^{-1}$ 25°	0°	Eact. Kcal.	Log PZ	Rel. Rate[b]
$(CH_3)_2CHCO_2C_2H_5$	—	43.7 ± 2.1	5.23 ± 0.14	13.8	7.8	2.5
IV. $R = C_2H_5$, $n = 3$	6.15	24.0 ± 0.8	3.09 ± 0.07	13.3	7.2	1.4
IV. $R = C_2H_5$, $n = 4$	6.15	187 ± 1	30.6 ± 0.5	11.8	6.9	11
IV. $R = C_2H_5$, $n = 5$	6.30	40.9 ± 1.3	7.39 ± 0.27	11.1	5.8	2.4
IV. $R = C_2H_5$, $n = 6$	6.35	17.2 ± 0.2	3.23 ± 0.16	10.9	5.2	1.0

[a] In 47% ethanol-water; pK_a's at 25°. [b] Relative rates at 25° to rate of cyclohexyl ester = 1.0.

TABLE II

PHYSICAL CONSTANTS OF ESTERS

Ester	B.P.	n_D^{25}	$\gamma_{c}{}^{a}{}_{o}$
$(CH_3)_2CHCO_2C_2H_5$	52°/80 mm.	1.3878	—
IV. $R = C_2H_5$, $n = 3$	70°/80 mm.	1.4403	1690
IV. $R = C_2H_5$, $n = 4$	85°/85 mm.	1.4245	1700
IV. $R = C_2H_5$, $n = 5$	75°/28 mm.	1.4340	1705
IV. $R = C_2H_5$, $n = 6$	95°/30 mm.	1.4380	1705

[a] Carbonyl stretching for carbon tetrachloride solutions in cm.$^{-1}$

carboxylic acids are thus weaker than the corresponding cyclopropane and cyclobutane acids. Moreover it has recently been suggested[7] that the steric environment of a saturated substituent on a cyclopentane ring (in its "envelope" form) is little different from that on a cyclohexane ring, and in both cases the pair of equatorial hydrogen atoms on the α-carbon atoms are placed near to the equatorial substituent. Since the electronic and steric nature of these two rings are very similar the cyclopentyl and cyclohexyl esters (IV. $R = C_2H_5$, $n = 5,6$) hydrolyzed at similar rates, and at a rate little different from that of ethyl isobutyrate.[8] This similarity should be contrasted with the large difference (51-fold) in the rates of saponification of ethyl isobutyrate and ethyl 3-ethylbutyrate (diethylacetate),[9] the open-chain analogue of the ring esters and this is no doubt due to the rigid forms of the ring which hold the carbon chains back from the carbethoxyl group.

The small difference between the rates of saponification of the cyclopentyl and cyclohexyl esters (IV. $R = C_2H_5$, $n=5 > n = 6$) are of the same magnitude as that found in the reaction of the cycloalkyl methyl bromides with phenoxide ion (I. $n = 5 < n = 6$)[3a] and the solvolysis of the cycloalkyl dimethylcarbinyl chlorides (II. $n = 5 > n = 6$),[3b] although the absolute orders are different.

The values of the energies of activation and the log PZ factor (Table I) were of the same order as those found for other saturated esters.[10] These values generally increased with increasing ring size but the order of the energies of activation was $3 \sim i\text{-Pr} > 4 > 5 \sim 6$, whereas that for the log PZ factors was $i\text{-Pr} > 3 > 4 \sim 5 > 6$. The higher energies of activation for the cyclopropane and cyclobutane carboxylic esters (IV. $R = C_2H_5$, $n = 3, 4$) reflect the higher dissociation constants of the corresponding acids although no linear relationship existed between the logarithms of the rates of saponification and the pK_a's, illustrating the fact that electronic and steric effects are not readily separable for aliphatic compounds.

EXPERIMENTAL

Acids. Cyclohexane, cyclopropane, and cyclobutane carboxylic acids were commercial samples (Eastman-Kodak Company and Aldrich Chemical Company). Cyclopentane carboxylic acid was prepared by the hydrogenation of cyclopentene carboxylic acid[11] in acetic acid using platinum oxide or by the oxidation of cyclohexanone with hydrogen peroxide in *t*-butyl alcohol in the presence of selenium dioxide.[12]

Esters. The acids (10–15 g.) were esterified by refluxing 3–5 hr. with anhydrous ethanol (25 ml.) and benzene (75 ml.) using concd. sulfuric acid (0.2 ml.) as catalyst, and removing the water continuously with a Dean-Stark separator. The esters were thoroughly washed with 10% sodium carbonate solution before distillation. The physical constants were in good agreement with literature values, and are given in Table II. The infrared spectra were determined with a Baird K-2 instrument using sodium chloride optics and carbon tetrachloride as solvent.

Hydrolyses. 95% Ethanol was purified by refluxing with zinc dust and sodium hydroxide and diluted with freshly boiled distilled water to give an aqueous ethanol of d_{25}^{25} 0.9316 or 41.2% ethanol. Ester (0.2–0.3 g.) was dissolved in about 85 ml. aqueous ethanol, placed in a constant temperature bath for at least 0.5 hr., 0.18*N* sodium hydroxide (10 ml.) in the same solvent at the same temperature added, and the solution rapidly made up to 100 ml. Aliquots (10 ml.) were withdrawn at intervals, added to an excess of 0.026*N* hydrochloric acid and the excess acid titrated with 0.020*N* sodium hydroxide using phenolphthalein as indicator. The hydrolyses were carried out in triplicate or quadruplicate and the average values with their mean errors are

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[8] A slower rate of saponification of ethyl cyclohexane carboxylate as compared to ethyl isobutyrate has also been noted in 85% ethanol at 25° (ratio 2.2:1). H. A. Smith and H. S. Leverson, *J. Am. Chem. Soc.*, **62**, 2733 (1940).

[9] *Cf.* W. Hückel, *Theoretical Principles of Organic Chemistry*, Elsevier, New York, 1958, vol. II, p. 738.

[10] D. R. Thomas and H. B. Watson, *J. Chem. Soc.*, 3958 (1956).

[11] O. H. Wheeler and I. Lerner, *J. Am. Chem. Soc.*, **78**, 63 (1956).

[12] G. B. Payne and C. W. Smith, *J. Org. Chem.*, **22**, 1680 (1957).

given in Table I. The energies of activation and the log PZ values were determined from the Arrhenius equation. The values of E act. are considered to be accurate to ±0.2 kcal. and the log PZ factors to ±0.2.

Dissociation constants. These were determined by potentiometric titration using the same sample of aqueous ethanol as used in the hydrolyses. The values reported in Table I are the mean of duplicate determination which differed by 0.05 unit.

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Formation and Properties of Isocyanates Derived from Amino Ester Hydrochlorides

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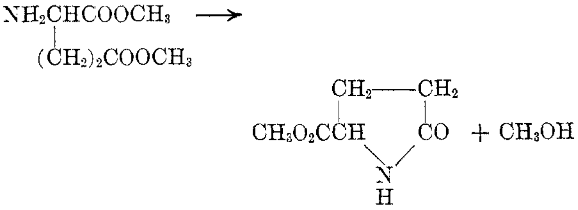
The usual methods for preparing isocyanates from amino ester hydrochlorides fail in many cases. A new, rapid procedure, uncomplicated by secondary reactions, is described for forming isocyanates derived from 2-, 3-, 6-, and 11-amino ester hydrochlorides. It was found that 2-isocyanato esters are activated towards reaction with active hydrogen compounds.

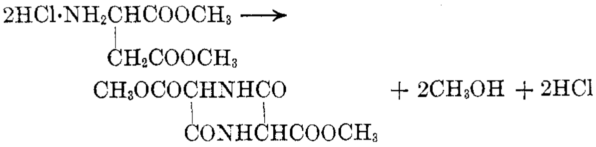
Although hundreds of isocyanates were known previous to the last twenty years, they were of only little technological interest. More recently, as a result of industrial applications, these substances have become the object of intensive research.[1] One method has dominated their synthesis, *i.e.*, the reaction of phosgene with amine hydrochlorides.

$$COCl_2 + RNH_2{\cdot}HCl \longrightarrow RNHCOCl + 2HCl$$

$$RNHCOCl \longrightarrow RNCO + HCl$$

Usually by this procedure, the amine salt is suspended in a refluxing diluent into which phosgene is passed. After allowing a reaction time of several hours, the product is isolated by distillation. However, hydrochlorides of certain amino esters undergo secondary reactions under these conditions. Isocyanates cannot be prepared efficiently, for example, from hydrochlorides of esters of glutamic or aspartic acid by this procedure unless the quantities are small, *i.e.*, less than 0.4 mole. Although isocyanates derived from these and other α-amino esters have been reported in 85–97% yields, they were produced in only 10–20 g. quantities.[2] Reaction of phosgene with 0.25, 0.5, and 2 moles of dimethyl glutamate hydrochloride gives 80, 60, and 30% yields, respectively. Phosgenation of three moles of diethyl aspartate hydrochloride yields no isocyanate. These results are attributed partly to the competing reaction of cyclization. We have isolated the corresponding pyrrolidone in high yield and small amounts of the diketopiperazine in these two cases, respectively. Indeed, 5-carbethoxy-2-pyrrolidone is reported to be obtained in 80% yield by heating the base, diethyl glutamate, for twenty minutes.[3]





Following the method of Siefken,[4] ethyl isocyanatoacetate can be prepared from twenty moles of glycine ethyl ester hydrochloride in 85% yield by phosgenation in toluene. Similarly, the isocyanate derived from three moles of methionine ethyl ester hydrochloride is obtained in 84% yield. However, reaction of phosgene with one mole of glycine isopropyl or isobutyl ester hydrochloride gives only a 5–10% yield of the isocyanate.

We have found that isocyanates can be prepared smoothly from hydrochlorides of amino esters in unlimited amounts by a general, *continuous* procedure. By this method, a solution of the salt is passed down a packed, heated column countercurrent to a stream of phosgene. The reaction temperature is the reflux temperature of the solvent, 1,2,3-trichloropropane (b.p. 155°). The reaction time within the apparatus is less than one minute. This method is somewhat similar to that described for other continuous reactions.[5]

Methyl, ethyl, isopropyl, *n*-butyl, and isobutyl α-isocyanato esters have been prepared in this way

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