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THE ALKALINE HYDROLYSIS OF METHYL 4-HYDROXYTETRAHYDROFURAN-2-CARBOXYLATES

AN EXAMPLE OF THE INTRAMOLECULAR NEIGHBOURING HYDROXYL GROUP CATALYSIS

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Abstract—The kinetics of the hydrolysis of methyl 4-hydroxy and methyl 4-methoxytetrahydrofuran-2-carboxylates has been studied. It is shown that saponification assisted by an intramolecular neighbouring hydroxyl group has higher enthalpy of activation and larger entropy of activation. These results suggest that the saponification of esters in aqueous medium is an electrophilic (H_2O)-nucleophilic ($OH^{\ominus}$) catalytic reaction.

IN THE course of synthesis of DL-demethylmuscarines,[4] it was found that methyl *cis*-4-hydroxytetrahydrofuran-2-carboxylates on treatment with dimethylamine are converted into 4-hydroxytetrahydrofuran-2-carboxylic acid dimethylamide 2–3 times faster than the *trans*-isomer. Similar nucleophilic reactions in rigid alicyclic esters promoted by an hydroxyl group in a favourable position in the same molecule have been reported.[5] It is considered that this facilitated solvolysis is related to the intramolecular hydrogen bonding between the hydroxyl group and either the carbonyl- or alkyl-oxygen, and a mechanism, based on IR spectroscopy and a qualitative rate comparison, has been proposed.[6] Recently, Bruice and Fife[7] showed that in the facilitated saponification of cyclopentanediol monoesters and esters of the norbornane series, the kinetics of these reactions are characterized by larger positive values of enthalpy and entropy of activation. As there is little data on this type of solvolysis in other systems, the kinetic data on the hydrolysis of 4-hydroxy-tetrahydrofuran-2-carboxylic esters is presented and the nature of intramolecular hydroxyl group catalysis discussed.

RESULTS

The hydrolysis rates of the esters, I–IV (Table 1) were measured at various temperatures. The solvent system used was 50 vol. % dioxan in water, and the rate was followed by acid-alkali titration with a pH-indicator. In the alkaline hydrolysis, the rate is nearly proportional to the concentration of the ester and of alkali

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[4] A. Ichihara, the Doctorate thesis, Faculty of Science, Hokkaido University (1962), *Bull. Chem. Soc. Japan* **33**, 1015 (1960).

[5a] H. B. Henbest and B. J. Lovell, *J. Chem. Soc.* 1965 (1957);

[b] S. M. Kupchan, P. Slade, R. J. Yong and G. W. A. Milne, *Tetrahedron* **18**, 499 (1962); S. M. Kupchan, W. S. Johnson and S. Rajagopalan, *Tetrahedron* **7**, 47 (1959);

[c] H. G. Zachau and W. Karau, *Chem. Ber.* **93**, 1830 (1960);

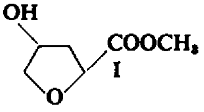
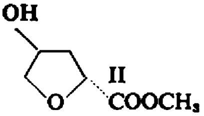
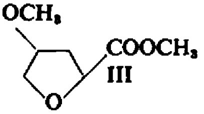
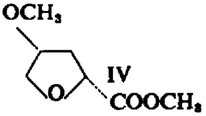
[d] M. J. Allen, *J. Chem. Soc.* 4904 (1960).

[6] See 5*a*, 5*b* and R. West, J. J. Korst and W. S. Johnson, *J. Org. Chem.* **25**, 1976 (1960).

[7] T. C. Bruice and T. H. Fife, *Tetrahedron Letters* No. 8, 263 (1961); *J. Amer. Chem. Soc.* **84**, 1973 (1962).

(sodium hydroxide), and the second order rate constant, k_2, obtained. The acidic hydrolysis rate is represented as the first order rate constant divided by the acid (HCl) concentration, $k_1/(\mathrm{HCl})$. Figs. 1, 2 and 3 show the plots of the saponification rate constant, k_2, versus 1/T (T, abs. temp) for esters I (Fig. 1), II and IV (Fig. 2) and III (Fig. 3) respectively. In Table 2 the Arrhenius' activation energy (E_a), frequency factor (log A) and the entropy of activation ($\Delta S^{\ddagger}$) are given for each ester. Accuracy of each value is ±10%.

TABLE 1. ALKALINE HYDROLYSIS RATES IN 50% AQUEOUS DIOXANE

Ester	k_2 at −2·7° l./mole. sec.	Relative rates −8·0°	−2·7°	20°*
 I	1·5	1·1	1·6	7·4
 II	0·92	1·0	1·0	1·0
 III	0·18	0·18	0·20	0·35
 IV	1·3	1·3	1·4	2·2

* Calculated from the observed rates.

ACIDIC HYDROLYSIS RATES IN 50% AQUEOUS DIOXANE

Ester	$10^4 k_1/(\mathrm{HCl})$, l./mole. sec. 40°	50°	60°
I	3·1	5·5	—
II	—	6·8	12

DISCUSSION

(a) *Alkaline hydrolysis*

Inspection of Table 1 and comparison of Figs 1–3 reveal that the rate of *cis*-hydroxy ester (I) is largely dependent upon the reaction temperature. Thus, I reacts slightly faster than II at −8°, 1·6 times at −2·7° and 7·4 times at 20°. Still higher temperatures increase the rate of I as compared with that of II.

The rates of esters II–IV have temperature-dependence similar to one another but smaller than that of ester I. In methoxy esters *trans*-isomer IV reacts 6–7 times

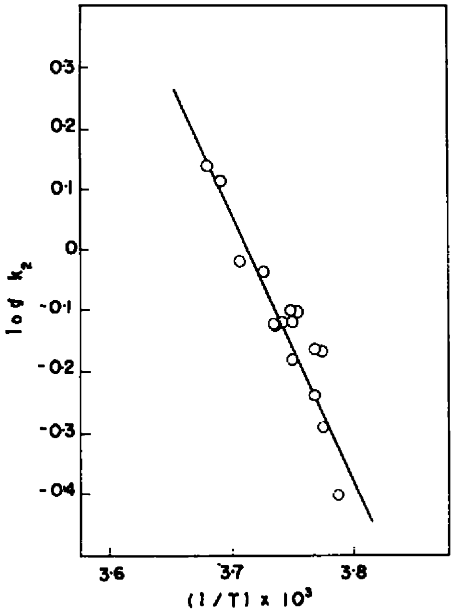


FIG. 1. Plot of log k_2 versus 1/T for alkaline hydrolysis of ester I.

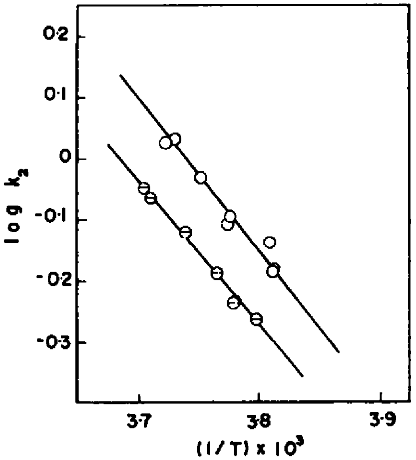


FIG. 2. Plots of log k_2 versus 1/T for alkaline hydrolysis of esters II (⊖) and IV (—○—).

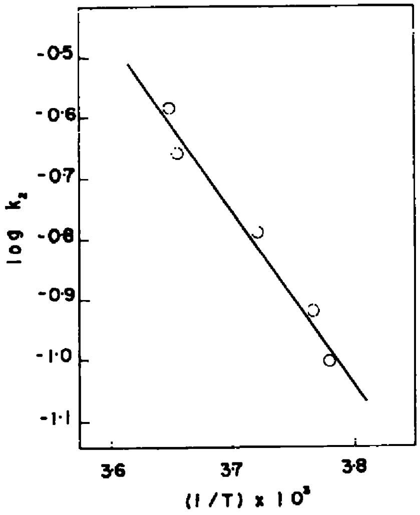


FIG. 3. Plot of log k_2 versus 1/T for alkaline hydrolysis of ester III.

faster than *cis*-isomer III. This shows that the *cis*-methoxyl group exerts steric hindrance on the approach of the hydroxide ion towards the ester group. An increase in the rate of hydrolysis by methylation of the hydroxy ester II is probably due to a small variation in the conformation of the tetrahydrofuran ring.

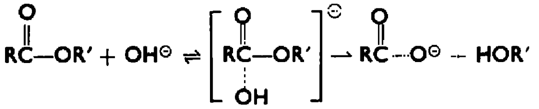
Table 2 shows that ester I is characterized by large positive values for the enthalpy ($E_a \fallingdotseq \Delta H^{\ddagger}$) and entropy ($\Delta S^{\ddagger}$) of activation as compared with other esters. Thus,

TABLE 2. E_A, LOG A AND THE ENTROPY OF ACTIVATION OF HYDROLYSIS IN 50% AQUEOUS DIOXANE

	Alkaline			Acidic	
Ester	E_a kcal/mole	Log A	$\Delta S^{\ddagger}$ e.u.	E_a kcal/mole	Log A
I	20	17	+14	12	4·8
II	11	8·5	−20	12	4·7
III	13	9·7	−16	—	—
IV	12	10	−15	—	—

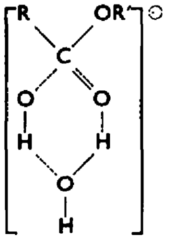
ester I possesses a large $\Delta H^{\ddagger}$ of 20 kcal/mole and ester II, III and IV possess $\Delta H^{\ddagger}$ values of 11, 13 and 12 kcal/mole, respectively. Evidently, the large value of $\Delta H^{\ddagger}$ for I is compensated by its large $\Delta S^{\ddagger}$ of 14 e.u. at sufficiently high temperature and the free energy of activation is minimized. In other words, the rate of I, as distinct from esters II, III and IV, is assisted by the intramolecular neighbouring hydroxyl catalysis and is controlled by the entropy of activation. It is recognized that this tendency is general for intramolecular catalysis in the nucleophilic reaction of carboxylic acid derivatives.[8] Consequently, a mechanism in which the enhanced rate of intramolecular hydroxyl group catalysis is ascribed to the lower enthalpy of activation[6] is incorrect.

Usually it is accepted that the saponification of ordinary esters proceeds through a mechanism (1), in which the participation of water molecules in the transition state is not considered.

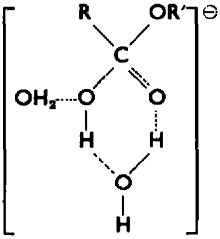


$$\mathrm{R\overset{\overset{O}{\|}}{C}{-}OR' + OH^{\ominus} \rightleftharpoons \left[R\overset{\overset{O}{\|}}{\underset{\underset{OH}{\vdots}}{C}}{-}OR'\right]^{\ominus} \rightarrow R\overset{\overset{O}{\|}}{C}{-}O^{\ominus} - HOR'} \qquad (1)$$

It is well known that solvation is an important factor in determining rate and equilibrium in solution and in fact, transition states involving water molecules such as (2a) and (2b) have been proposed.[9] It is, therefore, more reasonable to explain



(2a)



(2b)

the present results by taking into account the solvation by water of both initial and of transition states. The process of the alkaline hydrolysis of *cis-* and *trans*-hydroxy esters would then be described as scheme A and B respectively, where (H_2O) denotes

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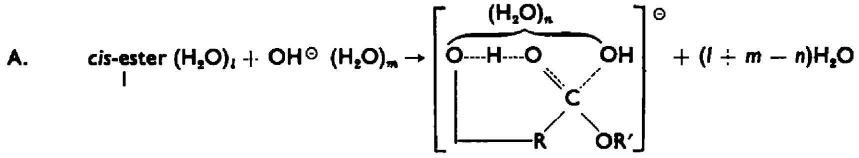
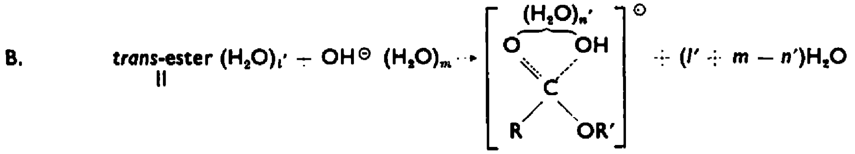
[8] M. L. Bender, *Chem. Rev.* **60**, 53 (1960).

[9] K. J. Laidler and P. A. Landskroener, *Trans. Faraday Soc.* **52**, 200 (1965); Y. A. K. Syrkin and I. I Moiseev, *Uspekhi Khim* **27**, 717 (1958).

water molecules within the solvation shell.



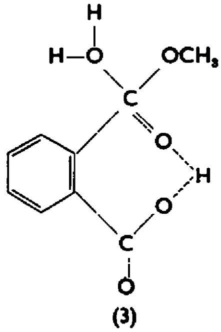
transition state A



transition state B

In these schemes, l is almost identical with l', since under the experimental conditions, intramolecular hydrogen bonding in the *cis*-isomer is inhibited by the presence of surrounding polar solvent molecules. On the other hand, n is certainly smaller than n', since in the transition state A, where the intramolecular hydrogen bonding become possible owing to the negative charge created around the (original carbonyl) oxygen atom, the negative charge is dispersed through the hydrogen bond as shown, while in the transition state B, in which intramolecular hydrogen bonding is lacking, negative charge is not dispersed. Since the extent of solvation is thus larger in transition state B than in A, $\Delta H_A^‡$ is larger than $\Delta H_B^‡$ and $\Delta S_A^‡$ is more positive than $\Delta S_B^‡$.[7,10]

The hydrolysis of methyl hydrogenphthalate in the neutral pH has been explained as nucleophilic catalysis[11] or general basic catalysis[8] by the intramolecular carboxylate ion, but should be regarded as electrophilic catalysis by the intramolecular carboxylic



(3)

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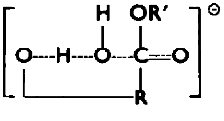
[10] An alternative, equally satisfactory mechanism is that which involves a general base catalysis as expressed by a transition state below.



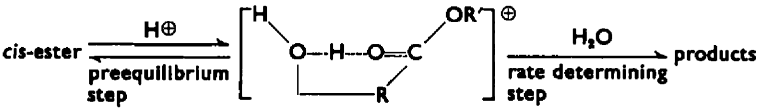
It is difficult to differentiate these two mechanisms from our experimental results. However, mechanism A is more plausible, since Bruice and Fife[7] have shown that *cis*-cyclopentane 1,3-diol monoacetate is hydrolyzed through the specific base-general acid catalysis mechanism by examining the kinetic solvent isotope effects.

[11] M. L. Bender, F. Chloupek and M. C. Neveu, *J. Amer. Chem. Soc.* **80**, 5384 (1958).

group, similar to the present case, as shown in (3). That the above catalysis occurs in the neutral pH is probably due to the strong acidity of carboxyl group.

(b) *Acidic hydrolysis*

Table 1 shows that in ester I, whose rate and activation parameters are substantially the same as those of ester II, the acidic hydrolysis is not facilitated. This agrees with other observations [5b] on the rate of acidic hydrolysis of the compounds with an intramolecular hydrogen bonded ester group. The absence of the facilitation can be accounted for by the generally accepted two step mechanism for the acidic hydrolysis. Participation, if any, of the *cis*-oriented hydroxyl group, in agreement with the base catalysed reaction, can be formulated as follows:



In comparison with the *trans*-ester, formation of the protonated intermediate is favourable for the *cis*-isomer, where the positive charge is more widely dispersed and the electro-striction of solvent molecules is smaller. In the second step, however, the situation is reversed the nucleophilic attack of water molecules being hindered, owing to the reduced positive charge at the carbonyl carbon atom. Consequently, $\Delta F^{\ddagger}$ will not be lowered or elevated as compared with a case where participation of hydroxyl group does not operate. The similarity of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ in esters I and II suggests that $\Delta F^{\ddagger}$ is not lowered in the above mechanism for *cis*-ester (I) and its hydrolysis proceeds through a route analogous to that of II.

EXPERIMENTAL

Materials

cis-, *and* trans-*4-Hydroxytetrahydrofuran-2-carboxylic acid.* 4-Hydroxytetrahydrofuran-2,2-dicarboxylic acid monohydrate[11] (42 g) in 420 ml water and decarboxylated in an autoclave at 150–160° for 80 min. The reaction mixture was evaporated to dryness and the residue extracted with hot ethyl acetate. On cooling the solution, the crude crystalline product separated out. After repeated fractional crystallization, *cis*-4-hydroxytetrahydrofuran-2-carboxylic acid (9·8 g, 34%), m.p. 129–130·5° was separated from the less soluble fraction, and *trans*-4-hydroxytetrahydrofuran-2-carboxylic acid (6·0 g, 21%), m.p. 143–144°, from more soluble fraction respectively.

Methyl cis-*4-hydroxytetrahydrofuran-2-carboxylate* (I) was prepared from *cis*-4-hydroxytetrahydrofuran-2-carboxylic acid in quantitative yield by esterification with diazomethane in ether–MeOH and purified by distillation under red. press., b.p. 77–78°/1·2 mm. This compound showed an absorption max in the IR at 3482 cm^{-1} in CCl$_4$ (0·0026 mole/l)[4], attributable to an intramolecular hydrogen bonded hydroxyl group. (Found: C, 49·22; H, 6·87. Calc. for C$_6$H$_{10}$O$_4$: C, 49·31; H, 6·90%.)

Methyl trans-*4-hydroxytetrahydrofuran-2-carboxylate* (II) was obtained by the same method as I; b.p. 95–98/2·5 mm. The compound has IR absorption bands at 3620 and 3482 cm^{-1} in dil. CCl$_4$ (0·0053 mole/l.), due to both a free hydroxyl group and to an intermolecularly associated hydroxyl group.[4] (Found: C, 49·27; H, 7·15. Calc. for C$_6$H$_{10}$O$_4$: C, 49·31; H, 6·90%).

Methyl cis-*4-methoxytetrahydrofuran-2-carboxylate* (III) was prepared from I by a modified

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[11] Prepared according to the Matsumoto and Ichihara's procedure, from allyl bromide and ethyl malonate. (T. Matsumoto and A. Ichihara, *Bull. Chem. Soc. Japan*, **33**, 1015 (1960).) Our preparation differs from Traube's in melting behavior: m.p. (dec.) 103–105° (cf. W. Traube, *Ber. Dtsch. Chem. Ges.* **37**, 4540 (1904)) and its analysis fits the formula C$_7$H$_{10}$O$_7$.

method of Bonner.[13] A mixture of I (2·0 g), MeI (100 ml), freshly prepared Ag_2O (45 g) and anhydrous Na_2SO_4 (10 g) was heated under reflux in a 300 ml flask equipped with a condenser for 2 days. After addition of a further quantity of Ag_2O and MeI, heating was continued for a further 2 days. After removal of solid material and excess MeI, the residue was submitted to fractional distillation under red. press. to give III (1·5 g, 69%), b.p. 66°/3 mm. This compound shows only one sharp peak by gas chromatography (reoplex 400-celite 1 m column, at 190°). The IR spectrum (liquid film) shows maxima at 2830 (methoxyl group), 1755 and 1733 cm^{-1} (ester group). The NMR spectrum showed these signals (in $CDCl_3$): a quartet at τ 5·55 (1H, J 7·3, 5·5 c/s C_2 proton): a singlet at 6·09 (3H, C_5 methylene proton and C_4 proton): a singlet at 6·33 (3H, methoxycarbonyl group): a singlet at 6·81 (3H, methoxyl group): a multiplet at 7·75 (2H, C_3 methylene protons).[14] (Found: C, 52·25; H, 7·54. $C_7H_{12}O_4$ requires: C, 52·49; H, 7·55%).

Methyl trans-*4-methoxytetrahydrofuran-2-carboxylate* (IV). This compound was prepared by the same method as III: b.p. 74°/3 mm. The IR absorption spectrum (liquid film) showed maxima at 2830 (methoxyl group), 1755, 1740 (ester group) and 890, 810 cm^{-1} (absent in the *cis*-isomer). It showed a single peak on the gas chromatography, and had following peaks in the NMR spectrum: (in $CDCl_3$): a triplet at τ 5·49 (1H, J 7·95 c/s C_2 proton): a singlet at 6·08 (3H, C_5 methylene proton and C_4 proton): a singlet at 6·33 (3H, methoxycarbonyl group): a singlet at 6·76 (3H, methoxyl group): a multiplet at 7·88 (2H, C_3 proton). (Found: C, 52·59; H, 7·57. $C_7H_{12}O_4$ requires: C, 52·49; H, 7·55%).

General procedure for rate measurement. Saponification experiments were made between 0° and −11°, using about 0·014N NaOH (50 vol. %-dioxane–50 vol. % water). The concentration of ether in solution was 0·010–0·013 mole/l. In one 50 ml flask with glass stopper the weighed ester was placed and in another 50 ml flask the required quantity of the alkali solution (standardized). These flasks were plugged and kept in a bath at the reaction temp. After about 30 min the alkali solution was poured into the flask containing the ester, and mixed thoroughly. At proper time intervals an aliquot of 4 ml was taken by a syringe from the flask and quickly put into the HCl aq to quench the reaction, and the solution titrated with the standard alkali.

In the experiments on acidic hydrolysis, HCl (0·03–0·04 N) in 50% dioxane–50% water was used as a catalyst, and aliquots were directly titrated with the standard alkali solution.

Dioxane used as solvent was refluxed with Na metal for 3 days and distilled.

Acknowledgments—We wish to thank Drs. T. Masamune and T. Takeshita for helpful discussions and to Dr. T. Stephen for correcting the manuscript.

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[13] W. A. Bonner, *J. Amer. Chem. Soc.* **73**, 3126 (1951).

[14] The absorption of $CHCl_3$ at τ 2·73 was used as internal standard.