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THE NATURE OF NEIGHBORING HYDROXYL GROUP ASSISTANCE IN THE ALKALINE HYDROLYSIS OF THE ESTER BOND

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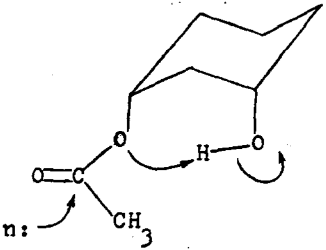
IT is now a well established fact that *cis*-cyclohexanediol monoacetates and (a,a) 1,3-cyclohexanediol monoacetates undergo alkaline hydrolysis with assistance of the neighboring hydroxyl group.[2-6] The mechanism suggested for the facilitation is that of Henbest and Lovell[2] (1).



(1)

In order to shed further light on the mechanism of facilitation we have determined the nature of the internal hydrogen bonding (in CCl_4 at high dilution; for methodology see refs. 2 and 7), as well as the hydrolytic

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[2] H.B. Henbest and B.J. Lovell, J.Chem.Soc. 1965 (1957).

[3] S.M. Kupchan, W.S. Johnson and S. Rajagopalan, *Tetrahedron* **7**, 47 (1959).

[4] S.M. Kupchan, and W.S. Johnson, *J.Amer.Chem.Soc*. **78**, 3864 (1956).

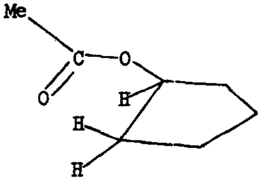
[5] S.M. Kupchan and C.R. Narayanan, *J.Amer.Chem.Soc*. **81**, 1913 (1959).

[6] S.M. Kupchan, P. Slade and R.J. Young, *Tetrahedron Letters* No.24,22 (1960).

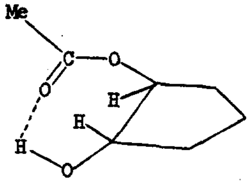
[7] R. West, J.J. Korst and W.S. Johnson, *J.Org.Chem*. **25**, 1976 (1960).

Hydrolysis In H_2O at 78° (μ=1.0M; k_r relative)

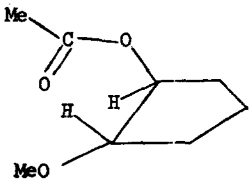
Dotted lines show hydrogen bond



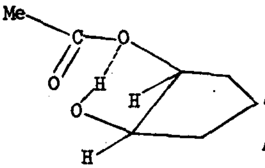
k_r 1.0
$\Delta H^\ddagger$ 11.3
$\Delta S^\ddagger$ -31.6



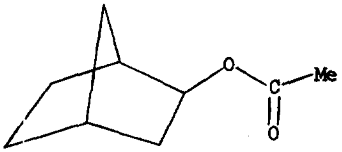
k_r 21.4
$\Delta H^\ddagger$ 15.3
$\Delta S^\ddagger$ -14.2



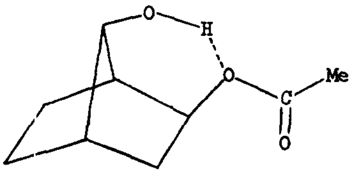
k_r 3.2
$\Delta H^\ddagger$ 11.9
$\Delta S^\ddagger$ -27.6



k_r 47.3
$\Delta H^\ddagger$ 19.1
$\Delta S^\ddagger$ -1.7



k_r 1.0



k_r 20.4
$\Delta H^\ddagger$ 16.8
$\Delta S^\ddagger$ -11.4

CHART I.

constants and associated activation parameters for the alkaline hydrolysis of a number of cyclopentane and norbornane acetates (Chart I).

Inspection of the data presented in Chart I as well as the temperature dependence of $\Delta S^{\ddagger}$ reveals the following:

(1) Alkaline hydrolysis is facilitated by a neighboring hydroxyl group in both the *vic*-cyclopentanediol monoacetates and in *exo*-2-acetoxy-*syn*-7-hydroxynorbornane. The facilitation is not due to an inductive effect (compare *trans*-hydroxy to *trans*-methoxycyclopentyl acetate).

(2) The facilitation is characterized by a large positive change of both $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$. The compensation by $\Delta H^{\ddagger}$ is not sufficient (78°) to prevent $\Delta F^{\ddagger}$ becoming more negative due to the overwhelming importance of $-T\Delta S^{\ddagger}$.

(3) The extent of facilitation is markedly temperature dependent and is only of the order 2 to 3x at 25°.

(4) The mechanism proposed by Henbest and Lovell is incorrect since marked enhancements of alkaline hydrolysis of esters must be ascribed to an increase in the rate constant associated with the attack of the $^{\ominus}OH$ on the ester carbonyl.[8] Also, and of greater significance, is the finding that the *trans* as well as the *cis* cyclopentanediol monoacetates exhibit facilitation. The Henbest mechanism could not apply to the *trans* ester.

(5) For the alkaline hydrolysis of ethyl acetate the $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ values associated with transfer from water to ethanol-water mixture resembles the $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ values noted on substitution of a neighboring hydroxyl group. Thus, ethyl acetate hydrolysis is slower in ethanol-water at 25° than in water but at 78° it should be faster in ethanol-water than in water.[9]

[8] T.C. Bruice and U.K. Pandit, *J.Amer.Chem.Soc*. **82**, 5858 (1960).

[9] Extrapolated from the data of J.E. Potts and E.S. Amis, *J.Amer.Chem.Soc*. **71**, 2112 (1949).

We suggest that the facilitation associated with the presence of a neighboring hydroxyl group is due to a microscopic medium effect and/or stabilization of the transition state associated with the attack of the hydroxide ion.