Effect of Internal Hydrogen Bonding on the Reactivity of the Hydroxy-group in Esterification under Phase-transfer Catalysed Conditions

By WIESŁAW SZEJA

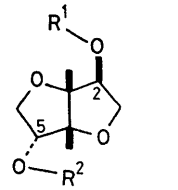
(*Institute of Organic Chemistry and Technology, Silesian Polytechnical University, 44–100 Gliwice, Poland*)

Summary Hydroxy-groups susceptible to forming an internal hydrogen bond show a diminished reactivity in esterification with acid chlorides under phase-transfer catalysed conditions.

IN reactions of carbohydrates with acid chlorides in pyridine intramolecular hydrogen bonding can often be used to explain the selectivity[1] and it has been suggested that the intramolecularly hydrogen-bonded hydroxy-group undergoes esterification more rapidly.[2] It was recently reported that treatment of alohols with acid chlorides under phase-transfer catalysed (P.T.C.) conditions[3] provides a simple method for preparing esters.[4] Continuing our investigations on P.T.C. esterification we have examined the effect of

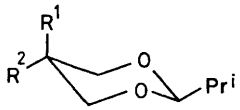
internal hydrogen bonding on the reactivity of hydroxy-groups.

The model compound examined was 1,4:3,5-dianhydro-D-glucitol (**1a**) which is conformationally rigid since it contains two *cis*-fused tetrahydrofuran rings. In this compound, only the *endo*-5-hydroxy-group can form an intramolecular hydrogen bond with the ring oxygen atom in the 4-position.[2] Treatment of (**1a**) with an equimolar amount



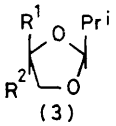
(1)

a; $R^1 = R^2 = H$
b; $R^1 = H$, $R^2 = PhCO$
c; $R^1 = PhCO$, $R^2 = H$
d; $R^1 = H$, $R^2 = Ts$
e; $R^1 = Ts$, $R^2 = H$



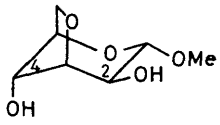
(2)

a; $R^1 = OH$, $R^2 = H$
b; $R^1 = H$, $R^2 = OH$



(3)

a; $R^1 = CH_2OH$, $R^2 = H$
b, $R^1 = H$, $R^2 = CH_2OH$



(4)

of benzoyl chloride under P.T.C. conditions followed by chromatography on silica gel yielded the diester (12%), the 2-*O*-ester (**1c**) (46%), and the 5-*O*-ester (**1b**) (17%), together with a small amount of starting sugar. The effect of hydrogen bonding on the reactivity of hydroxy-groups was further elucidated in a series of competitive reactions. The monoesters (**1b**) and (**1c**) were allowed to react with one molar proportion of benzoyl chloride or toluene-*p*-sulphonyl chloride. The results collected in Table show that the hydroxy-group at C-2 reacts more rapidly than the 5-OH group which is susceptible to internal hydrogen-bond formation. It is interesting that the reverse is the case when the esterification with acid chlorides is carried out in pyridine.[2] The relative rates of esterification of cyclic acetals derived from glycerine and isobutyric aldehyde, determined in the following competitive reactions, show that hydrogen-bonded hydroxy-groups are less reactive. Thus, the more easily esterified *trans*-5-hydroxy-2-isopropyl-1,3-dioxan (**2b**) exists to a large extent in conformations with the hydroxy-group non-hydrogen bonded,[5] whereas the *cis*-isomer (**2a**),[5] and *cis*- (**3a**) and *trans*-4-hydroxymethyl-2-isopropyl-1,3-dioxolan (**3b**) show the presence of an internal hydrogen-bonded hydroxy-group (i.r. absorptions at 3598 and 3600 cm^{-1} respectively).

TABLE. Relative rate for competitive esterification at 20 °C[a].

Alcohols	Acid chloride[b]	Relative rate
(**1b**) + (**1c**)	BzCl	$k_{1b}/k_{1c} = 4{\cdot}1$
(**1b**) + (**1c**)	TsCl	$k_{1b}/k_{1c} = 3{\cdot}8$
(**2b**) + (**2a**)	BzCl	$k_{2b}/k_{2a} = 15{\cdot}7$
(**2b**) + (**3a**)	BzCl	$k_{2b}/k_{3a} = 1{\cdot}9$
(**2b**) + (**3b**)	BzCl	$k_{2b}/k_{3b} = 1{\cdot}5$

[a] The reaction mixture comprised the alcohols (2 mmol each) in benzene (10 ml), with Bu_4NCl (0·2 mmol), 20% aqueous sodium hydroxide solution saturated with sodium chloride (3 ml), and the acid chloride (2 mmol). [b] Bz = PhCO; Ts = *p*-$MeC_6H_4SO_2$.

It is possible that the decreased reactivity of alkoxide ions formed from hydrogen-bonded hydroxy-groups under P.T.C. conditions in the presence of alkali in some cases is partly due to steric hindrance. However, steric considerations alone cannot account for the results observed in the esterifications. Thus, from competitive reactions using (**2b**) and (**3a**) or (**2b**) and (**3b**) we have found that a secondary hydroxy-group was acylated in preference to the primary one. Similarly, esterification of methyl 3,6-anhydro-α-D-mannopyranoside (**4**) with an equimolar amount of toluene-*p*-sulphonyl chloride under P.T.C. conditions resulted in favoured esterification of the axially oriented hydroxy-group. For this compound, with i.r. absorptions near 3565 and 3600 cm^{-1}, the first frequency can be assigned to the more strongly hydrogen-bonded equatorial hydroxy-group, O_2–H···O_3 (*cis-ortho ae*).[6]

The decrease in the acidity of the hydroxy-group on formation of an internal hydrogen bond may influence the relative reactivity of this group in the P.T.C. esterification. In the complex salt Q^+ (3 ROH·OH)$^-$ ($Q^+ = R_4N^+$, see ref. 7) transferred into an organic phase, the charge is somewhat spread over several oxygen atoms, structure (A),[7] and equilibrium favours the alkoxide ion derived from the more acidic alcohol to some extent.[8]

$$3\ ROH{\cdot}OH^- \rightleftharpoons 2\ ROH{\cdot}HOH{\cdot}OR^-$$

(A)

We thank the Polish Academy of Sciences for a grant.

(*Received*, 10*th November* 1980; *Com.* 1206.)

[1] A. H. Haines, *Adv. Carbohydr. Chem. Biochem.*, 1975, **33**, 11, and references therein.
[2] R. U. Lemieux and A. G. McInnes, *Can. J. Chem.*, 1960, **38**, 136; K. W. Buck, A. B. Foster, A. R. Perry, and J. M. Webber, *J. Chem. Soc.*, 1963, 4171; K. W. Buck, J. M. Duxbury, A. B. Foster, A. R. Perry, and J. M. Webber, *Carbohydr. Res.*, 1966, **2**, 122.
[3] M. Makosza, *Pure Appl. Chem.*, 1975, **43**, 439, and references therein; E. V. Dehmlow, *Angew. Chem. Int. Ed. Engl.*, 1977, **16**, 493, and references therein.
[4] P. J. Garegg, T. Iversen, and S. Oscarson, *Carbohydr. Res.*, 1977, **53**, C5; W. Szeja, *Synthesis*, 1979, 821, 822; 1980, 402.
[5] N. Baggett, M. A. Bukhari, A. B. Foster, J. Lehmann, and J. M. Webber *J. Chem. Soc.*, 1963, 4157.
[6] A. J. Michell and H. G. Higgins, *Tetrahedron*, 1965, **21**, 1109.
[7] C. M. Starks and C. Liotta, 'Phase Transfer Catalysis Principles and Techniques,' Academic Press, New York–San Francisco–London, 1978, p. 21, and references therein.
[8] J. Murto, 'The Chemistry of the Hydroxyl Group,' ed. S. Patai, Interscience, London–New York–Sydney–Toronto, 1971, part 2, pp. 1087—1115, and references therein.