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CONCERNING A NEW METHOD FOR THE DETERMINATION OF ABSOLUTE CONFIGURATION

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IN a recent communication[1] a new method for the determination of the absolute configurations of alcohols has been proposed, which depends on their preferential esterification by one antipode of a racemic acid. The procedure quoted is the reaction of an alcohol with an excess of a racemic acid chloride or anhydride in pyridine. The excess acylating agent is then hydrolysed giving the partially resolved acid, whose rotation is measured. The argument employed to interrelate the stereochemistries of the optically active acid and the alcohol, assumes that the alcohol is preferentially esterified by the acyl stereoisomer which yields the ester having the lesser internal steric interactions. <u>This argument is only valid if the esterification reaction is thermodynamically controlled</u>. Under the quoted conditions this is unlikely to be the case.

A similar case, namely the esterification of a racemic alcohol in the presence of an optically active base, has recently been discussed.[2] Esterifications with an acid anhydride in the presence of a tertiary amine proceed via the formation of the acylammonium cation.[3] The subsequent

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[1] A. Horeau, <u>Tetrahedron Letters</u> No. 15, 506 (1961).

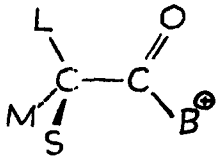
[2] C.W. Bird, <u>Tetrahedron</u>. In press.

[3] In some cases esterification with acid chlorides under these conditions proceeds via ketene formation.[4] This probably accounts for the observed[1] disparity between esterifications with acid anhydrides and chlorides.

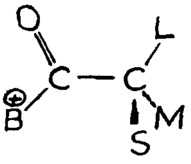
[4] G. Pracejus, <u>Liebigs Ann.</u> **622**, 10 (1960).

reaction of this with the alcohol is the rate determining step. Thus, in considering such kinetically controlled esterifications attention should be focussed on the interactions in the transition state for the reaction of the alcohol molecule with the acylammonium cation.

The preferred conformations of the stereoisomeric acylammonium cations will be I and II, where L, M and S indicate the relative sizes of the substituent groups, namely large, medium and small. The alcohol molecule, e.g. III, will approach the carbonyl group of the acylammonium ion from the less hindered side. In the case of I and II this is the frontside, leading to the formation of the intermediates IV and V respectively. The non-bonded interactions that arise in the formation of IV and V will be different. If the L.M.S.C -group is sterically larger than B^+ then the



I



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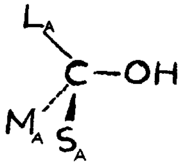

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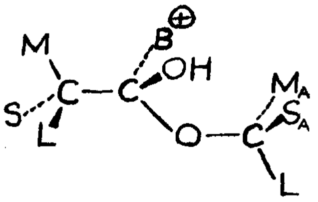
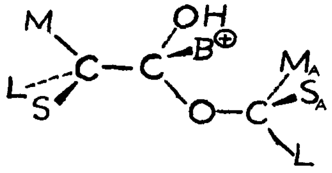


IV



V

interactions involved in the formation of V will be less than for IV. Hence the acylammonium cation II should react faster with the alcohol III leaving a preponderance of unreacted I. Obviously the stereoisomeric alcohol would be esterified faster by I. The converse results will obtain if B^+ is sterically larger than L.M.S.C -.

Although application of these principles to the quoted data leads to the same absolute configurations as previously deduced it is clear that the argument previously employed is incorrect and would generally lead to wrong assignments. The concurrence in the present case is fortuitous.