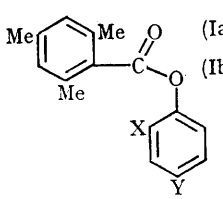
The Nucleophilic Centre of the Amide Group

By R. M. TOPPING and D. E. TUTT

(*The Chemical Laboratory, The University of Sussex, Brighton*)

RECENT interest in the possibility of involvement of the peptide backbone of protein in the catalytic function of enzymes has led to conjecture over the nucleophilic character of the amide group. The use of Raman,[1] infrared,[1,2] ultraviolet,[1,3] and nuclear magnetic resonance spectroscopy[4] and the determination of dipole moments,[1] pK_a-values[5] and complexing constants with molecular iodine[6] has resulted in conflicting opinion as to the basic centre of the amide group. Although many examples[7] of participation of the amide group in reactions at ester and amide linkages have been observed, a quantitative comparison of the relative effectiveness of nucleophilic attack by the amide group acting through oxygen (*O*-attack) or through nitrogen (*N*-attack) has often been obscured by the possibility for the corresponding intermediates to yield a common product. We now describe a system in which the cleavage of a sterically hindered ester linkage is effected solely (the competitive intermolecular hydroxide ion-catalysed reaction being sterically blocked) and very effectively by a suitably located amide group in such a way that the nature of the products is indicative of the mode of participation of the amide group.

For both the esters (Ia) and (Ib), a study of the influence of variation in pH upon the rate of



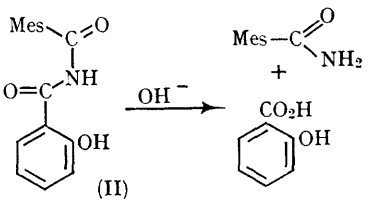
(Ia) X=H Y=$CONH_2$

(Ib) X=$CONH_2$, Y=H

scission of the ester bond reveals a first-order dependence with respect to both hydroxide ion and ester concentrations. However, under comparable conditions (pH 10·20, μ = 1·0 M, T = 30°, solvent 9·5% ethanol–water) whereas the half-life for cleavage of the ester bond in the ester (Ia) is more than eight weeks, the cleavage of the ester bond in the ester (Ib) has a half-life of less than five minutes. At high pH, the ester (Ia) was quantitatively* converted into mesitoic acid and

* Shown by precise superimposition of the spectrum of the reaction mixture at t_∞ upon the spectrum of a mixture of components corresponding to 100% reaction.

p-hydroxybenzamide. Pseudo-first-order kinetics were observed to 82% reaction. In contrast, the ester (Ib) undergoes quantitative rearrangement to the imide (II). Close adherence to pseudo-first-



(II)

(Mes=2,4,6-trimethylphenyl)

order kinetics up to 88% completion of reaction and the linear relationship between changes in optical density at any two given wavelengths between 200 and 450 mμ indicated the absence of any intermediate (with the possible exception of one at low steady state) between the ester and the imide. The rate constants were shown to be virtually independent of buffer (carbonate) concentration. The final step, the hydroxide ion-catalysed hydrolysis of the imide can occur at only one of the imide carbonyl groups to give mesitamide (stable to further hydrolysis as a result of steric blocking of the carbonyl group) and salicylic acid *only* (isolated, identified and shown spectrophotometrically to account for 100% of the initial ester). The ultimate production of a highly hindered amide from a relatively unhindered amide in 100% yield at ambient temperature in aqueous solution suggests that the steric hindrance to attack at the ester carbonyl group has been overcome by the intramolecular nucleophilic participation of the amide group acting entirely through nitrogen.

The high reactivity and selectivity of the carbonyl group in the structure (I) to attack by an amide group located at position X is also a feature of a variety of other groups when located at X.

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