The Mechanism of Ester Acidolysis

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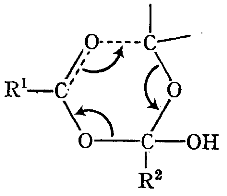
ACYL-OXYGEN cleavage of the ester function has been reported during the acidolysis of acetyltestosterone. The fact that acetyltestosterone did not change its configuration during reaction with [^{14}C]acetic acid in the presence of HCl was taken as evidence for acyl-oxygen cleavage.[1] We question the validity of this conclusion since retention of configuration is known to occur in S_Ni reactions.[2] If the mechanism of acidolysis involves formation of a tetrahedral intermediate, as commonly occurs in nucleophilic reactions of carboxylic acids,[3] a transition state (I) may be written that accounts for retention of configuration. However, this mechanism predicts that alkyl-oxygen cleavage takes place. A tetrahedral intermediate has previously been postulated for the acidolysis of esters,[4] but the mode of cleavage of the ester function has not been reported.



(I)

The data in the Table summarizes results of mass spectrometric analysis of *p*-toluic acid, ^{18}O-labelled *p*-toluic acid, methyl *p*-toluate, and ^{18}O-labelled methyl *p*-toluate, prepared from the labelled acid. The analysis involved the ratio of the $(m + 1)$ and $(m + 2)$ peaks of the parent ions.

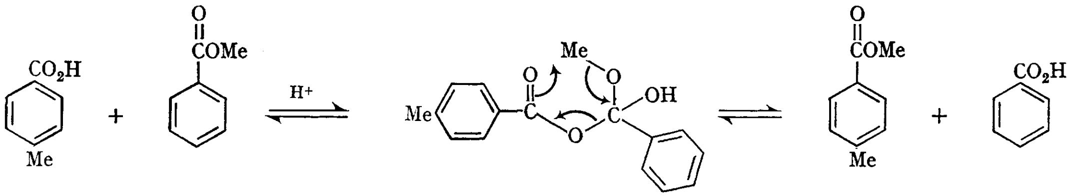
If acyl-oxygen cleavage were to occur during the reaction of methyl benzoate with ^{18}O-labelled *p*-toluic acid, the $(m + 1) : (m + 2)$ ratio for the resulting methyl *p*-toluate would be expected to fall halfway between the values for the ^{16}O ester and the ^{18}O ester (prepared by reaction of the labelled acid with diazomethane) (Table). On the other hand if alkyl-oxygen cleavage occurs [transition state (I)] this ratio should be very close to that of the [^{18}O]ester prepared with diazomethane.

Comparison of mass $(m + 1)$ *and* $(m + 2)$ *peaks from* ^{18}O *acid and ester with* ^{16}O *acid and ester peaks.*

Compound	$(m + 1 : m + 2)$	^{16}O : ^{18}O
^{16}O acid[a]	6·44	> 2·16
^{18}O acid[b]	2·98	
^{16}O ester[c]	5·50	> 2·06
^{18}O ester[d]	2·67	

[a] Obtained from Distillation Products Industries, recrystallized from hexane–methylene chloride. [b] Prepared from *p*-toluoyl chloride and ^{18}O (1·6%) enriched H_2O. [c] Prepared from MeOH–H_2SO_4 treatment of *p*-toluic acid. [d] Prepared from ^{18}O containing acid and diazomethane.

When methyl benzoate (5·0 g.) was allowed to react with ^{18}O-labelled *p*-toluic acid (1·0 g.) at 170° in the presence of concentrated H_2SO_4 (0·1 g.) for 30 min., methyl *p*-toluate was isolated from the reaction mixture (about 50% conversion). The ratio of the mass $(m + 1) : (m + 2)$ peaks was 2·58, in close agreement with the value of 2·67 (Table) found for the ester prepared with diazomethane. Our results are most consistent with the following mechanism.



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[3] M. L. Bender, *Chem. Rev.*, 1960, **60**, 53.

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