Boron Fluoride–Alcohol Alkylations. III. Stereochemistry of Alkylation of Benzene with 2-Propanol-1-d_3[1]

Sir:

A knowledge of the stereochemical consequence of a Friedel–Crafts alkylation of an aromatic hydrocarbon is an essential component of any theory of reaction mechanism, yet no unambiguous study has been reported heretofore.[2] Alkylations with alcohols and boron fluoride are advantageous because starting material and product are not affected by the catalyst.[1b] The reaction of optically active 2-butanol with benzene and boron fluoride has been shown to give *sec*-butylbenzene with 99% racemization during the alkylation step.[3] However, the significance of this result is clouded by the known rapid rearrangements of secondary systems in this reaction[1b]; thus, even an encumbered 2-butyl cation could give the appearance of racemization by rapid equilibration of the cationic charge between the 2- and 3-positions.[2]

This ambiguity is avoided with the isopropyl system which is known not to rearrange—only one secondary cation position is available. Mislow, O'Brien, and Schaefer's[4] preparation of optically active 2-propanol-1-d_3, $\alpha^{21.6}D$ +0.280 ± 0.007° (*l* 1, neat), was repeated. The expected alkylation product was synthesized from optically pure (−)-3-phenylbutanoic acid. The α-hydrogens were exchanged for deuterium by treatment of the methyl ester with sodium methoxide in methanol-*d*. Reaction of the acid with iodine and lead tetraacetate[5] gave 1-iodo-2-phenylpropane-1-d_2, which on reduction with lithium aluminum deuteride, gave 2-phenylpropane-1-d_3, $\alpha^{22}D$ +0.48 ± 0.02° (*l* 1, neat). From the known stereochemistry of the starting acid,[6] the (+)-hydrocarbon is assigned the *R* configuration.

Reaction of the (+)-(*S*)-2-propanol-1-d_3 with benzene and boron fluoride at 5° gave 2-phenylpropane-1-d_3, $\alpha^{25}D$ +0.009 ± 0.005° (*l* 1, neat). A similar alkylation in a 60:40 benzene–nitromethane solvent at 50° gave the hydrocarbon with $\alpha^{25}D$ +0.033 ± 0.005° (*l* 1, neat). Hence, even in the absence of rearrangement, alkylation proceeds with >93% racemization and very little net inversion of configuration. This racemization is not due to prior racemization of alcohol or to subsequent racemization of product or to an equilibration with olefin. We conclude that the isopropyl cation intermediate in the alkylation is a largely free and unencumbered cation. The reaction is much like an SN1 solvolysis and has little of the character of a direct displacement reaction or of a π-complex with benzene.[1b,2]

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The Kinetics of the Trypsin-Catalyzed Hydrolysis of *p*-Nitrophenyl α-N-Benzyloxycarbonyl-L-lysinate Hydrochloride[1]

Sir:

Although the kinetics of the presteady state and steady state of the hydrolysis of the nonspecific substrate, *p*-nitrophenyl acetate, by α-chymotrypsin[2,3] and trypsin[4] have been delineated, a complete kinetic analysis of this kind had not been carried out for the corresponding hydrolysis of a specific substrate of these enzymes. This paper reports the first such reaction, the trypsin-catalyzed hydrolysis of *p*-nitrophenyl α-N-benzyloxycarbonyl-L-lysinate hydrochloride, which can be analyzed in terms of eq. 1 whose symbols

$$E + S \underset{}{\overset{K_s}{\rightleftharpoons}} ES \xrightarrow{k_2} ES' \xrightarrow[+\,P_1]{k_3} E + P_2 \qquad (1)$$

have been defined previously.[3]

Previous work with α-chymotrypsin reactions[5] indicated that both the presteady-state and steady-state reactions with trypsin were probably dependent on a basic group of $pK_a \sim 7$. Therefore the present kinetic analysis was carried out at pH 2.66. At this low pH, the rate of the presteady-state reaction was indeed slow, slow enough in fact to be measured on a Cary Model 14 spectrophotometer. Using these conditions we were able to observe the major part of the presteady-state liberation of *p*-nitrophenol (occurring in about the first 30 sec. of reaction), followed by a slow, steady-state (zero-order) liberation of *p*-nitrophenol (Figure 1). Presteady-state rate constants at different initial substrate concentrations were calculated by graphically extrapolating the steady-state straight line of a *p*-nitrophenol *vs.* time curve and plotting the logarithm of the difference between this extrapolated line and the experimental curve as a function of time. The experimental points give good straight lines, the slope of which yields the first-order rate constant, *b* (Table I). The definition of *b*, based on eq. 1 and $S_0 \gg E_0$, is[3]

$$b = \frac{(k_2 + k_3)S_0 + k_3K_s}{S_0 + K_s} \qquad (2)$$

A plot of $1/b$ *vs.* $1/S_0$, which yields a straight line in the α-chymotrypsin-catalyzed hydrolysis of *p*-nitrophenyl acetate, gives instead for the present data a very definite curvature. The obvious explanation in terms of eq. 2 is that the condition $(k_2 + k_3)S_0 \gg k_3K_s$ is not satis-

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