ium-type ion. The enormous accelerating effect of α-cyclopropyl groups is clearly evident. Comparing further, the rate of ionization of I-OPNB is 32 times that of the simpler analog without the cyclopentano rings,[6b] V-OPNB, or the value estimated for the dicyclopropylcarbinyl analog[3a] VI-OPNB, 7.5×10^5 times that of the bicyclic analog[8b] VII-OPNB containing only one cyclopropane ring, and 3×10^7 times that of the allylic cyclohexenyl ester[8b] VIII-OPNB. The relative rates of solvolysis in 80% acetone at 25°, estimated from available rate data, are listed with the structural formulas.

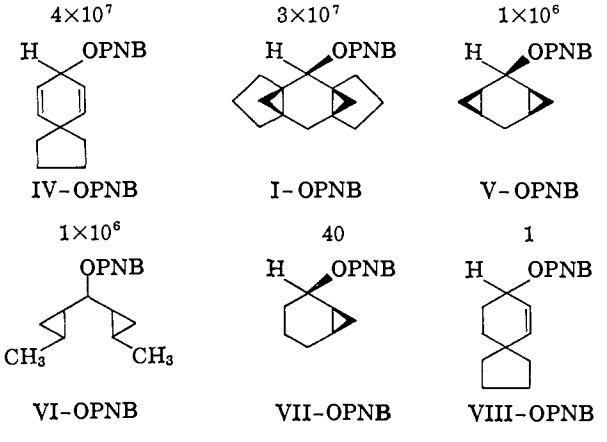
As regards relative ionization rates of the *cis* and *trans* epimers, that of the *cis*-I-OAc is *ca.* twice as high as that of the *trans*-II-OAc. The free-energy difference between the *trans* transition state and the *cis*, RT ln 200, is in the same direction and slightly greater than the ground-state free energy difference, *RT* ln 100, which we know from actual equilibration.[6a] The stereospecificity in alcohol product formation shows that the free-energy difference between *trans* and *cis* transition states in alcohol formation is also *RT* ln 200, the same as the difference between *trans* and *cis* acetate transition states.

Kinetic and thermodynamic control of products are, of course, correlated with reactivity[2b] by means of eq 1 and 2, where K measures thermodynamic control, (k_{II}/k_I) is a reactivity ratio R, and (k_{-I}/k_{-II}) is a partition factor P representing kinetic control or stereospecificity. Applying eq 2 to alcohol equilibration, we know exactly only the value of P, 200, from the solvolysis results. However, we can approximate R as *ca.* 1/2, the value from solvolysis of the acetates, and K as *ca.* 100 from equilibration of the acetates.

$$\text{II-X} \underset{k_{-II}}{\overset{k_{II}}{\rightleftharpoons}} \text{R}^+ \underset{k_{-I}}{\overset{k_I}{\rightleftharpoons}} \text{I-X} \qquad (1)$$

$$K = \frac{(\text{I-X})}{(\text{II-X})} = \left(\frac{k_{II}}{k_I}\right)\left(\frac{k_{-I}}{k_{-II}}\right) = RP \qquad (2)$$

It is interesting to compare the situation with the I and II epimers with that pertaining to the *i*- and epi-*i*-cholesteryl epimers.[2b] With I and II, the more stable epimer is slightly more reactive and is highly favored in kinetic product control. On the other hand, with the *i*- and epi-*i* derivatives, the less stable *i* epimer is more reactive and highly favored by kinetic product control. This illustrates the different possible blends of steric factors connected with the leaving (or incoming) group in ground and transition states and stereoelectronic factors connected with participation of the a–b and a–c cyclopropane bonding electrons in electron delocalization of the transition state.



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A Pictorial Description of the "Lock and Key" Theory[1]

Sir:

We wish to report a striking model for enzymatic specificity, the cycloamylose-catalyzed reactions of substituted phenyl esters. The cycloamyloses (cyclodextrins) approximate a torus and are capable of forming inclusion compounds in solution[2] with a variety of organic and inorganic substances. Furthermore, the cycloamyloses have been shown to impose both rate accelerations and decelerations on organic reactions, such as the acceleration of the cleavage of diphenyl pyrophosphate (with concomitant phosphorylation of the cyclodextrin)[3] and the deceleration of the hydrolysis of ethyl *p*-aminobenzoate.[4] We have investigated the effect of cycloamyloses on the rate of reaction of substituted phenyl acetates in order to determine the stereochemical requirements of the interaction in these systems.

The alkaline hydrolysis of a series of substituted phenyl acetates was followed spectrophotometrically by observing the liberation of the phenol at pH 10.6. The accelerating effects of cyclohexaamylose and cycloheptaamylose on the rates of some of these reactions are shown in Table I. The accelerations are dependent on the concentration of cycloamylose, approaching a maximum (saturation) value at high concentration, as has been noted before.[3,4] The data were treated by a variation of Michaelis–Menten kinetics[5] to determine the rate constant of the bound species, k_c, and the (dissociation) constant of binding, K_d, in Table I. We have also observed competitive inhibition of the cycloamylose rate accelerations[6] by addition of molecules such as *m*-chlorobenzoate ion[7] to the reaction mixture. The observations of saturation and competitive inhibition suggest that the reaction proceeds through a cycloamylose–ester complex.

The cycloamylose accelerations (k_c/k_u) are often large and are markedly substituent dependent. In contrast, the accelerations of these hydrolyses by 0.06 M α-methyl glucoside are small (10–20%) and are independent of substituent. Although the alkaline hydrolysis of substituted phenyl acetates follows a Hammett relationship with $\rho = 1.07$ (correlation coefficient

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Table I. Maximum Rate Accelerations and Binding Constants in the Cycloamylose-Catalyzed Hydrolysis of Phenyl Acetates[a,b,d-f]

Acetate	Hydroxide ion rate,[g] $k_u \times 10^4$, sec^{-1}	Cyclohexaamylose: $k_c \times 10^2$, sec^{-1}	Cyclohexaamylose: k_c/k_u	Cyclohexaamylose: $K_d \times 10^3$, M	Cycloheptaamylose: $k_c \times 10^2$, sec^{-1}	Cycloheptaamylose: k_c/k_u	Cycloheptaamylose: $K_d \times 10^3$, M
Phenyl	8.04	2.5	32	27	...	...	...
o-Tolyl	3.84	0.75	20	21	...	...	...
m-Tolyl	6.96	7.2	103	21	...	...	...
p-Tolyl	6.64	0.26	4	14	...	...	...
3,5-Dimethylphenyl	5.80	12	200	16(13)[c]	5.0	84	9.0
m-*t*-Butylphenyl	4.90	13	260	2.0	12.2	249	<0.5
p-*t*-Butylphenyl	6.07	0.075	1.2	7.7	...	...	...
m-Chlorophenyl	19.1	26	~140	~6(4.8)[c]	4.5	23	3.9
m-Nitrophenyl	46.4				42.6	90	7.3
p-Nitrophenyl	69.4				6.9	8.9	6.4

[a] In pH 10.6 carbonate buffer, I = 0.2, 0.5% acetonitrile–water, 25.0 ± 0.2°; ester ~10^{-4} M. [b] Six to eight cycloamylose concentrations from 0.001 to 0.02 M were used for each experiment. [c] Determined by direct measurement of binding constant using ultraviolet spectrophotometry at pH 2.2 in aqueous solution at 25°: 3,5-dimethylphenyl acetate, 235 mμ; *m*-chlorophenyl acetate, 230 and 235 mμ. [d] These data are calculated on the basis of a 1:1 complex, which, however, has not as yet been rigorously proven. [e] The spectra of the products corresponded to the spectra of the phenols. [f] The *meta–para* specificity is largely lost in reactions with cyclooctaamylose. [g] The first-order rate constants were independent of initial ester concentration.

= 0.978), the Hammett plot of the acceleration of these reactions by the cycloamyloses shows an unprecedented scatter. These results indicate that the cycloamylose accelerations are dependent on steric factors. This stereochemical preference is most strikingly seen in the cyclohexaamylose-catalyzed reactions of *m*- and *p*-*t*-butylphenyl acetates: the ratio of the maximum cyclohexaamylose rate to the uncatalyzed rate for the *meta* isomer is 260-fold while it is 1.2-fold for the *para* isomer.

The stereochemical cause of these differential rate accelerations must lie in the stereochemistry of the complexes formed during reaction. There appears to be an approximate linear relationship between the logarithm of the binding constant and the molecular volume of the guest (as measured by the parachor). For the various *meta–para* pairs, however, the binding constant is only slightly dependent on structure, there being no simple relationship between rate acceleration and strength of binding—*only one between rate acceleration and stereochemistry of binding.*

An X-ray diffraction analysis of cyclohexaamylose[8] shows a torus consisting of six α-D-(+)-glucose units in their normal C1 conformation, with the hydroxyl groups forming crowns around the top and bottom of the torus. Corey–Pauling–Koltun models[9] reproduce this structure well and delimit an internal diameter of ~5 A. Models of the cyclohexaamylose complexes of *p*-*t*-butylphenyl and *m*-*t*-butylphenyl acetate, constructed on the assumption of maximum hydrocarbon interaction of the guest molecule in the void of the host, orient the plane of the phenyl ring parallel to the axis of the cavity. This description is borne out by the spectrum of *p*-*t*-butylphenol in the presence of cyclohexaamylose which resembles its spectrum in dioxane, an unoriented analog of the cavity.

Molecular models of the complexes indicate that the *secondary hydroxyl groups of the host are much closer to the carbonyl group of m-t-butylphenyl acetate than they are to the carbonyl group of p-t-butylphenyl acetate.* Thus, if the stereochemical features of the rate of accelerations are the result of a chemical interaction it must involve the interaction of the ester with the hydroxyl groups of the cycloamylose. The following communication[10] shows that the accelerations are indeed the result of such an interaction. The relative amount of this interaction is seen to be determined by the stereochemistry of the fit between guest and host in these relatively rigid systems. Thus the relative rates of reactions of this series are controlled by the stereospecific complexing postulated in the "lock and key" theory of enzymatic catalysis proposed by Fischer.[11]

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(12) The authors thank Professor Dexter French for a generous supply of cycloamyloses.
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The Mechanism of the Cycloamylose-Catalyzed Reactions of Phenyl Esters. A Model for Chymotrypsin Catalyses[1]

Sir:

Cycloamyloses accelerate the liberation of phenols from phenyl esters, exhibiting a stereospecificity which may result from an interaction of the hydroxyl groups of the host with the ester linkage of the guest in an inclusion complex of the two.[2] The present communication indicates that a chemical interaction does take place, involving a hydroxyl group of the cycloamylose acting as a nucleophile.

The reactions of several phenyl benzoates were examined here in order to investigate the fate of the acid portion of the ester in addition to the phenol portion. In the cyclohexaamylose- and cycloheptaamylose-catalyzed hydrolysis of *m*-chlorophenyl, *m*-nitrophenyl, and *m*-*t*-butylphenyl benzoates (Table I), two rate

(1) This research was supported by the National Science Foundation.
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