Selective Aromatic Substitution within a Cyclodextrin Mixed Complex

Sir:

The selectivity of enzyme-catalyzed reactions is due to the formation of an enzyme–substrate complex. Within such a complex, only certain substrate atoms are sterically accessible to attack. Organic reactions, by contrast, generally involve attack by simple reagents on those positions of a substrate which are intrinsically reactive. The most obvious difference is that biochemical reagents (enzymes) are almost always larger and more complex than the substrates, while the reverse is generally true in organic chemistry. However, a number of studies have been made of the hydrophobic binding of small molecules into the cavities of cyclodextrins (cycloamyloses).[1] Furthermore, these cyclic sugars have been shown to catalyze the hydrolysis of some phosphate[2] and carboxylic esters[3] which form mixed complexes. We have examined the possibility of directing the course of an aromatic substitution by carrying it out within the cyclodextrin cavity on a cyclodextrin–substrate complex. The results indicate not only that the cyclodextrin blocks all but one aromatic ring position to substitution, but also that it actively catalyzes substitution at the unblocked position.

Anisole, 10^{-4} *M* in H_2O, was treated for 12 hr at room temperature with 10^{-2} *M* HOCl (unbuffered, initial pH 4.7) in the presence of varying amounts of cyclohexaamylose (α-cyclodextrin). The relative yields of *o*-chloro- and *p*-chloroanisole were determined by vpc analysis and are listed in Table I. We have also determined the anisole–cyclodextrin dissociation constant to be $(3.72 \pm 0.5) \times 10^{-3}$ *M* at 25°, using the method of Cramer[1] and a Hildebrand–Benesi plot[4] (isosbestic points at 276 and 265 nm). The per cent of anisole bound at the various cyclodextrin concentrations is listed in Table I. From these data it can be seen that *para* chlorination becomes essentially the exclusive process in the presence of sufficient cyclodextrin, although in controls maltose had no effect on the product ratio. Models show that the anisole can fit into the cyclodextrin cavity as shown in Figure 1, so that the *ortho* positions are blocked but the *para* position is free and accessible to cyclodextrin hydroxyl groups.

Table I

Cyclohexaamylose, $M \times 10^3$	Chloroanisole product ratio, *p*:*o*	% anisole bound
0	1.48	0
0.933	3.43	20
1.686	5.49	33
2.80	7.42	43
4.68	11.3	56
6.56	15.4	64
9.39	21.6	72

However, this cannot be the whole story, since with only 72% of the anisole complexed, substitution is almost exclusively *para*. The data in Table I are fully consistent with a kinetic scheme in which the partial rate factor $k_{ortho\ \text{complex}}$ is zero, and $k_{para\ \text{complex}}/k_{para\ \text{free}}$ is 5.6 ± 0.8 (the error reflects uncertainty in the dissociation constant, and the least squares kinetic plot has only 3% deviation). The increase in rate within the nonpolar cyclodextrin cavity for a process in which charge develops in the transition state is not expected. The most obvious explanation is that the hydroxyl groups which rim the cavity are participating catalytically, perhaps by reaction with HOCl to form intracomplex hypochlorite groups which act as the true donors.

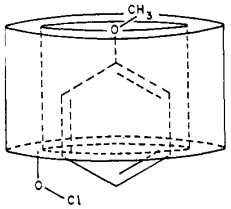

Figure 1. Schematic representation of an anisole molecule in the cavity of cyclohexaamylose. Eighteen hydroxyl groups (not shown) ring the mouths of the cavity, one of which is written as its hypochlorite ester to indicate a mechanism by which the increased rate of chlorination in the complex may be explained.

It is interesting that enzymatic chlorination of anisole shows no such increased specificity[5] as we have observed in our enzyme model but is instead apparently occurring with uncomplexed substrate. However, our system is a good model for more typical highly specific enzymatic reactions, and it may also represent a useful approach to specificity in synthetic chemistry.[6]

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(6) Support of this work by the National Institutes of Health is gratefully acknowledged.
(7) Public Health Service Predoctoral Fellow.

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Received February 14, 1969

Solvent Effects on a Probable Charge-Transfer Reaction. Inter- and Intramolecular Photoreactions of Tertiary Amines with Ketones

Sir:

Interest in the photoreduction of ketones by amines has very recently evolved into quantitative studies.[1-6] Specific bimolecular rate constants for interaction of ketone triplets with triethylamine have been estimated to exceed 10^8 M^{-1} sec^{-1} for benzophenone[1,4b] and to lie in the range 10^7–10^8 M^{-1} sec^{-1} for fluorenone[3,5] and *p*-aminobenzophenone.[2] The latter two ketones possess π,π^* lowest triplets, and the rate constants with

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